CLINICAL STUDY PROTOCOL

PRODUCT: GLASSIA

STUDY TITLE: A Phase 3/4 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

STUDY SHORT TITLE: Ph 3/4 GLASSIA Safety, Immunogenicity, and Bronchoalveolar Lavage Study

PROTOCOL IDENTIFIER: 471101

CLINICAL TRIAL PHASE 3/4

AMENDMENT 2: 2015 MAY 07
Replaces Amendment 1: 2015 JAN 19

ALL VERSIONS:
Amendment 2: 2015 MAY 07
Amendment 1: 2015 JAN 19
Original: 2011 JUL 05

OTHER ID(s)
NCT Number: Not Available
IND NUMBER: 14774

Study Sponsor(s): **Baxalta US Inc.**
One Baxter Way
Westlake Village, CA 91362
USA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Global Clinical Development
Baxalta US Inc.

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

**ALL SAEs ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (ECRF)
WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE ECRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT.**

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

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

- AE, Section 12.1
- SAE, Section 12.1.1.1
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	GLASSIA
Name of Active Ingredient	Alpha$_1$-Proteinase Inhibitor (Human)
CLINICAL CONDITION(S)/INDICATION(S) • GLASSIA is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of alpha$_1$-proteinase inhibitor (A1PI) (also known as alpha$_1$-antitrypsin [AAT] deficiency).	
PROTOCOL ID	471101
PROTOCOL TITLE	A Phase 3/4 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 3/4 GLASSIA Safety, Immunogenicity, and Bronchoalveolar Lavage Study
STUDY PHASE	Ph 3/4
PLANNED STUDY PERIOD	
Initiation	Q3 2015
Primary Completion	Q3 2017
Study Completion	Q3 2017
Duration	Approximately 2 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of the study is two-fold: (1) to further evaluate the safety and potential 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.	
Primary Objectives 1. To evaluate the effectiveness of the use of 5-micron in-line filter on the safety and potential immunogenicity of GLASSIA. 2. 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.	
Secondary Objective 1. To collect additional safety information for GLASSIA.	
Exploratory Objective [redacted]	

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	This Phase 3/4, 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 a dosage of 60 mg/kg BW/week (the dosing regimen that is currently approved by the Food and Drug Administration [FDA]) 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 [redacted] in the ELF. Once the target of 15 to 18 evaluable subjects has been 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 (defined as a total recovery of ≥20% of the instilled volume of saline) are obtained at both baseline and on-treatment BAL visits. 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. 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 [redacted] 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).

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 (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. 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 AEs 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: • 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 after the last infusion.

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 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

1. Antigenic A1PI levels in ELF
2. Functional A1PI (also known as anti-neutrophil elastase capacity [ANEC]) levels in ELF

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 following GLASSIA administration
3. Number (proportion) of subjects with treatment-emergent seroconversion or positive nucleic acid test (NAT) for parvovirus B19 (B19V)

Exploratory Outcome Measures

[redacted]

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) 15 to 18 evaluable subjects with acceptable BAL samples collected from both the baseline and on-treatment BAL visits (b) A minimum of 36 randomized subjects.
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:

1. Male or female subjects meeting the following age criteria:
   (a) For subjects who will undergo bronchoscopy/BAL procedures: 18 to 65 years of age at the time of screening.
   (b) For subjects who will be waived from undergoing bronchoscopy/BAL procedures (after adequate number of BAL evaluable subjects has been reached): 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, or other "at-risk" allelic combinations (excluding MS, MZ, and SZ).
3. Endogenous plasma (antigenic) A1PI level of <11 µM (A1PI measurement may be repeated for subjects with an initial screening A1PI level of 11 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, and/or evidence of airway obstruction which is not completely reversed with bronchodilator treatment at the time of screening.
5. 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.
6. 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.
7. 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.
8. The subject is willing and able to comply with the requirements of the protocol.
9. The subject must have pulmonary functions at the time of screening meeting both of the following:
   (a) Post-bronchodilator forced expiratory volume in 1 second (FEV1) ≥50% of predicted
   (b) If FEV_1 is >80% predicted, then FEV1/forced vital capacity (FVC) must be <0.7.

Note: Inclusion criterion #9 is not applicable to subjects who are enrolled after the target of 15 to 18 evaluable subjects has been reached and who are therefore not required to undergo the bronchoscopy/BAL procedures.

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, chronic bronchitis, mild bronchiectasis, and stable asthma).
2. The subject is experiencing or has a history of cor pulmonale.
3. The subject routinely produces more than one tablespoon of sputum per day.
4. The subject has a history of frequent pulmonary exacerbations (greater than 2 moderate or severe exacerbations within 52 weeks prior to screening; see Section 10.4 for the definition of moderate and severe exacerbations).
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 abnormalities (other than emphysema, chronic bronchitis, or mild bronchiectasis) detected on chest X-ray or CT scan at the time of screening. (Past records obtained within 52 weeks prior to screening may be used, if available.)
7. The subject has clinically significant abnormalities detected on a 12-lead electrocardiogram (ECG) performed at the time of screening. (Past records obtained within 26 weeks prior to screening may be used, if available.)
8. The subject has clinically significant congestive heart failure with New York Heart Association (NYHA) Class III/IV symptoms.
9. 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.
10. The subject has a history of lung or any other organ transplant, is currently on a transplant list, or has undergone major lung surgery.
11. The subject is receiving long-term around-the-clock oxygen supplementation. (The following are allowed: short-term use of oxygen supplementation [eg, for the management of acute COPD exacerbation], oxygen supplementation required during night time only, and supplemental O_2 with continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]).
12. Known history of hypersensitivity following infusions of human blood or blood components.
13. Immunoglobulin A (IgA) deficiency (<8 mg/dL at screening).
14. 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/mm^3
    f. Hemoglobin (Hgb) <9.0 g/dL
    g. Platelet count <100,000/mm^3
15. Ongoing active infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection at the time of screening.
16. 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.

17. 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.
18. The subject is a family member or employee of the investigator.
19. If female, the subject is nursing at the time of screening.
20. The subject has contraindication(s) to bronchoscopy such as recent myocardial infarction, unstable angina, other cardiopulmonary instability, tracheal obstruction or stenosis, moderate to severe hypoxemia or any degree of hypercapnia, unstable asthma, Stage 4 or 5 chronic kidney disease, pulmonary hypertension, severe hemorrhagic diathesis, and cervical C1/C2 arthritis.
21. The subject has had lung surgery which may interfere with bronchoscopy.
22. 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.
23. 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.
24. 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.

Note: Exclusion criteria #20, 21, 22, 23, and 24 are not applicable to subjects who are enrolled after the target of 15 to 18 evaluable subjects has been reached and who are therefore not required to undergo the bronchoscopy/BAL procedures.

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 a previous clinical study (Clinical Protocol 460502; Baxter Healthcare Corporation) for the evaluation of the effects of A1PI augmentation therapy with ARALAST NP on the levels of A1PI and other analytes in the ELF. 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]

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Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
˚C	Degree Celsius
˚F	Degree Fahrenheit
A1PI	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
CIs	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)
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation	Definition
EDC	Electronic data capture
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

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
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.[6; 8; 11; 13; 14; 15; 16; 17; 18] 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.[6; 11] 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 µM in subjects with A1PI deficiency of Pi*Z/Z genotype.[11]

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 1 dose-escalation and a Phase 2/3 pivotal clinical trial in a total of 65 individual subjects with severe A1PI deficiency.

The clinical lots used in the GLASSIA Phase 2/3 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 2/3 trial, as well as other commercially available A1PI products upon reconstitution of the lyophilized powder. During the Phase 2/3 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 2/3 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 insert and/or investigator's brochure [IB]).

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 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 and/or IB.

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 Phase 2/3 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 and/or IB.

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 and/or IB).

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 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 and/or IB.

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 further evaluate the safety and potential 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 potential 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 3/4, 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 a dosage of 60 mg/kg BW/week (the dosing regimen that is currently approved by the Food and Drug Administration [FDA]) 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 [redacted] in the ELF. Once the target of 15 to 18 evaluable subjects has been 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 (defined as a total recovery of ≥20% of the instilled volume of saline) are obtained at both baseline and on-treatment BAL.

Enrollment will be closed when both conditions are met:

(a) 15 to 18 evaluable subjects with acceptable BAL samples collected from both the baseline and on-treatment BAL visits

(b) A minimum of 36 randomized subjects.

If for any reasons the target of 15 to 18 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).

Table 8-1
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, 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 [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.

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 (unless the subject withdraws or is prematurely discontinued from the study), 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 after the last infusion.

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 following GLASSIA administration
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]

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 and Section 9.2) 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 15 to 18 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 biostatistician.

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 (in the US) 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 body weight at screening. The same dose (in mg) is to be administered to an individual subject throughout the course of treatment. Adjustments based on body weight changes during the course of the study are 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 and/or IB.

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 [Alpha$_1$-Proteinase Inhibitor (Human)]

Dose: 60 mg/kg BW/week

Dosage frequency: Once every week (± 2 days)

Treatment period: 25 weeks (ie, 25 planned infusions), to be followed by a 7 (± 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 subjects meeting the following age criteria:
   (a) For subjects who will undergo bronchoscopy/BAL procedures: 18 to 65 years of age at the time of screening.
   (b) For subjects who will be waived from undergoing bronchoscopy/BAL procedures (after adequate number of BAL evaluable subjects has been reached): 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, or other "at-risk" allelic combinations (excluding MS, MZ, and SZ)
3. Endogenous plasma (antigenic) A1PI level of <11 µM (A1PI measurement may be repeated for subjects with an initial screening A1PI level of 11 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, and/or evidence of airway obstruction which is not completely reversed with bronchodilator treatment at the time of screening.
5. 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.
6. 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.
7. 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.
8. The subject is willing and able to comply with the requirements of the protocol.

9. The subject must have pulmonary functions at the time of screening meeting both of the following:
   (a) Post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% of predicted
   (b) If FEV_1 is >80% predicted, then FEV_1/forced vital capacity (FVC) must be <0.7.

Note: Inclusion criterion #9 is not applicable to subjects who are enrolled after the target of 15 to 18 evaluable subjects has been reached and who are therefore not required to undergo the bronchoscopy/BAL procedures.

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, chronic bronchitis, mild bronchiectasis, and stable asthma).
2. The subject is experiencing or has a history of cor pulmonale.
3. The subject routinely produces more than one tablespoon of sputum per day.
4. The subject has a history of frequent pulmonary exacerbations (greater than 2 moderate or severe exacerbations within 52 weeks prior to screening; see Section 10.4 for the definition of moderate and severe exacerbations).
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 abnormalities (other than emphysema, chronic bronchitis, or mild bronchiectasis) detected on chest X-ray or CT scan at the time of screening. (Past records obtained within 52 weeks prior to screening may be used, if available.)
7. The subject has clinically significant abnormalities detected on a 12-lead electrocardiogram (ECG) performed at the time of screening. (Past records obtained within 26 weeks prior to screening may be used, if available.)
8. The subject has clinically significant congestive heart failure with New York Heart Association (NYHA) Class III/IV symptoms.
9. 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.
10. The subject has a history of lung or any other organ transplant, is currently on a transplant list, or has undergone major lung surgery.

11. The subject is receiving long-term around-the-clock oxygen supplementation. (The following are allowed: short-term use of oxygen supplementation [eg, for the management of acute COPD exacerbation], oxygen supplementation required during night time only, and supplemental O_2 with continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]).
12. Known history of hypersensitivity following infusions of human blood or blood components.
13. Immunoglobulin A (IgA) deficiency (<8 mg/dL at screening).
14. 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/mm^3
    f. Hemoglobin (Hgb) <9.0 g/dL
    g. Platelet count <100,000/mm^3
15. Ongoing active infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection at the time of screening.
16. 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.
17. 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.
18. The subject is a family member or employee of the investigator.
19. If female, the subject is nursing at the time of screening.
20. The subject has contraindication(s) to bronchoscopy such as recent myocardial infarction, unstable angina, other cardiopulmonary instability, tracheal obstruction or stenosis, moderate to severe hypoxemia or any degree of hypercapnia, unstable asthma, Stage 4 or 5 chronic kidney disease, pulmonary hypertension, severe hemorrhagic diathesis, and cervical C1/C2 arthritis.

21. The subject has had lung surgery which may interfere with bronchoscopy.
22. 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.
23. 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.
24. 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.

Note: Exclusion criteria #20, 21, 22, 23, and 24 are not applicable to subjects who are enrolled after the target of 15 to 18 evaluable subjects has been reached and who are therefore not required to undergo the bronchoscopy/BAL procedures.

9.3 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 acceptable 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. These subjects may be re-screened after the target enrollment of BAL evaluable subjects is completed. If acceptable BAL samples can be obtained during the baseline BAL visit but not from 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.

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. Randomization is to take place after the subject has met all eligibility criteria and, as applicable, the subject has 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 plasma A1PI level

Subjects must have A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, or Pi*Null/Null, or other "at-risk" allelic combinations (excluding MS, MZ, and SZ) AND plasma antigenic A1PI level of <11 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 plasma 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 plasma 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 days 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 >11 µM.

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.[19; 20] 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 (FEV_1 and FVC) are to be measured 30 ± 5 minutes following administration of a short-acting β-2 agonist bronchodilator (eg, a total of 400 µg of salbutamol [2 x 200 µg or 4 x 100 µg] or its equivalent). Spirometric measurements (FEV_1 and FVC) are to be performed in triplicate, and the highest value at each time point for each variable is to be used for analyses. The spirometry equipment is to be calibrated according to the manufacturer's recommendation and documented in a maintenance log. The same method for the calculation of predicted normal values will be applied for all subjects and assessment time points to maintain standardization.

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 ≥11 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)

Subjects who were discontinued early from the study due to failure to yield adequate baseline BAL samples will be allowed to rescreen after the target enrollment of BAL evaluable subjects is completed.

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 at 30 (± 15) 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 ºC (101 ºF)

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 and report the SAE as described in Section 2.

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 9.3.

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

10.3.3 Clinical Assessment Visits

Following Week 1 visit, subjects will be asked to return to the study site during Week 13 and Week 25 for on-treatment 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 bronchoscopy/BAL procedures. Bronchoscopy/BAL procedure will be waived for subjects who are enrolled after 15 to 18 BAL evaluable subjects have been obtained. An evaluable subject is defined as a subject who has successfully completed both the baseline and the on-treatment BAL visits, and has acceptable BAL sample (defined as a total recovery of ≥20% of the instilled volume of saline) collected from each visit.

Subjects will be asked to undergo the bronchoscopy/BAL procedures on 2 occasions: at baseline (prior to randomization) and following initiation of GLASSIA treatment for 12 to 14 weeks.

The baseline BAL visit must be conducted after verification of deficient plasma (antigenic) A1PI levels (below 11 μM) has been obtained. Subjects who have been receiving A1PI augmentation therapy prior to study entry must have plasma samples collected within 10 days prior to the baseline BAL visit for the measurement of plasma (antigenic) A1PI levels to verify the adequacy of the washout from A1PI therapy prior to performing BAL. The baseline bronchoscopy/BAL visit must be completed prior to randomization and within 48 hours prior to the first IP administration. In order for a subject to be randomized and remain in the study, the subject must have acceptable BAL sample (total recovery of ≥20% of the total original instilled volume of saline). 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 7 (± 1) days following the last IP infusion, but must be completed prior to the next IP infusion. Whenever possible, it is recommended that sufficient time (typically 24 to 48 hours) is allowed for the subject to recover from the bronchoscopy/BAL procedures prior to IP administration.

Subjects who have successfully completed the on-treatment BAL visit and have acceptable BAL samples will be considered as an 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. New subjects may be enrolled to achieve the target of 15 to 18 evaluable subjects, as necessary.

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

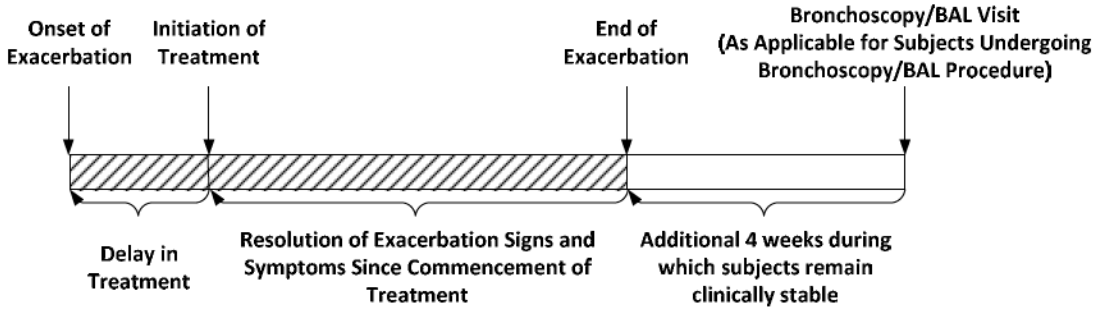
will remain in the hospital/clinic until, in the investigator's medical judgment, it is safe to discharge the subject. Subjects will be followed for post-BAL safety monitoring (ie, AEs and concomitant medications/non-drug therapies) at the study site or by telephone within 2 weeks after each BAL procedure.

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 and/or IB). 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 timing of the rescheduled BAL visit will follow the same requirements as described above for the on-treatment BAL visit.

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.[21; 22]

Figure 10-1
Exacerbation of COPD



If a subject experiences a moderate or severe COPD exacerbation and/or LRTI during the screening period, the 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 a 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 ≤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 A1PI 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.

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, IB, 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 Report Form and followed-up at estimated date of delivery and 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 provided SAE Report 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.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 20.2-1) and Section 12.1 above.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant electronic Case Report Form (eCRF) page(s) in English. Once the SAE has been recorded in the EDC system, the Sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24 hour timeline requirement (contacts and instructions to be provided in separate documentation). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAE report form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAE Report Form, if applicable) must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
    - Date of onset
    - (S)AE treatment (drug, dose, route of administration)
    - Causal relationship by the Investigator
    - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAE Report Forms)

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 AE CRF (and SAE Report Form if eCRF is not available). 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, nitrite, 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 an new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.6), 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 binding antibody (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 2 or more aliquots of approximately equal volume (at least one of the aliquots will serve as backup sample; see laboratory manual for further details):
  - 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 plasma A1PI levels at target of 11 µM or greater. Plasma samples for the determination of trough antigenic A1PI and functional A1PI (also known as ANEC) levels will be collected prior to the first IP infusion during Week 1, on the day of IP administration (must be collected 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 (°C or °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 at 30 (± 15) 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 ºC (101 ºF)

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 a previous clinical study (Clinical Protocol 460502; Baxter Healthcare Corporation) for

the evaluation of the effects of A1PI augmentation therapy with ARALAST NP on the levels of A1PI and other analytes in the ELF. 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.

$$Ho: \mu_d \leq 0$$

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

$$H1: \mu_d > 0$$

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 (Baxalta) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

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

15.6 Laboratory and Reader Standardization

Not applicable; 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.

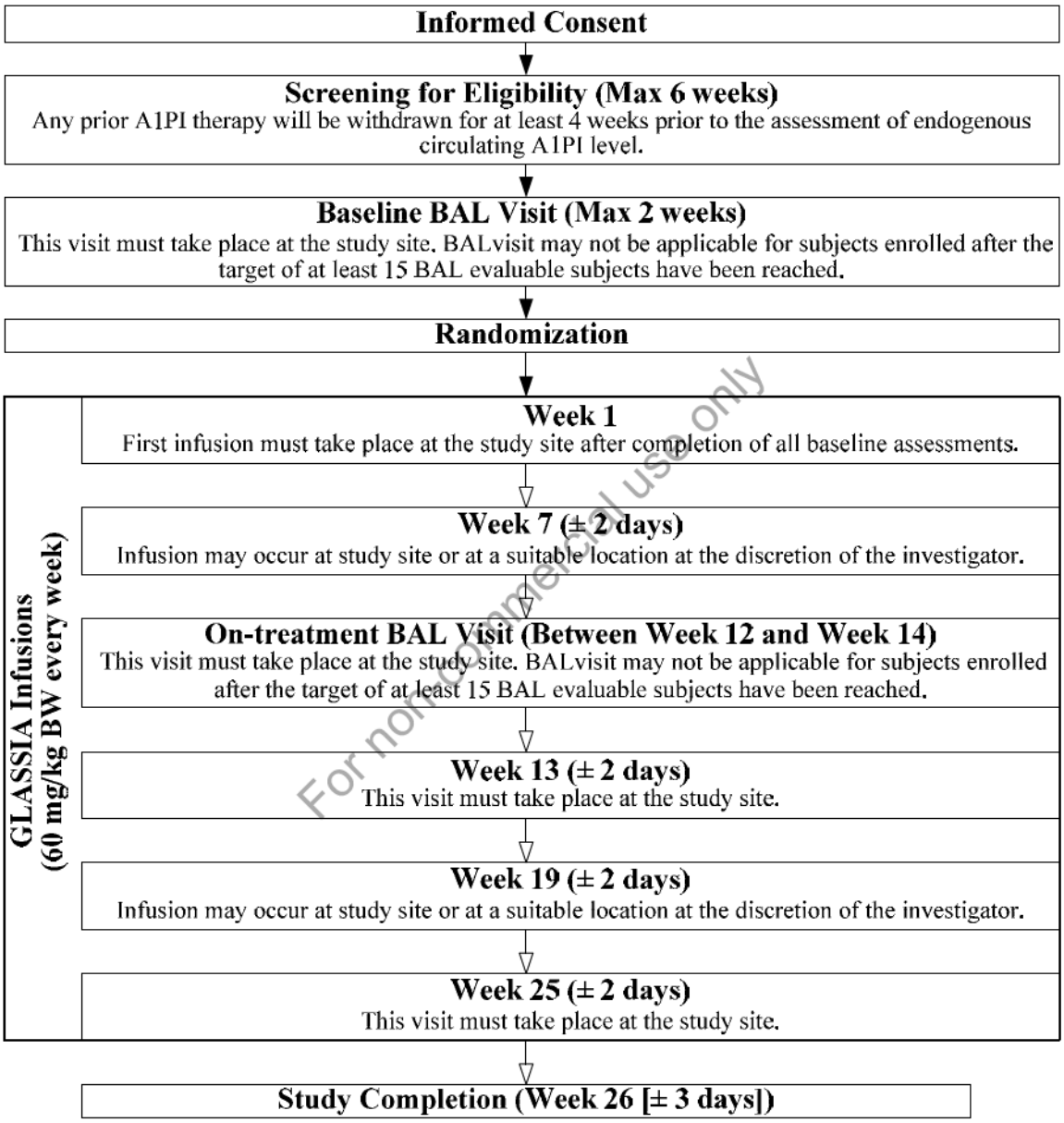
19. PUBLICATION POLICY

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

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 20-1
Study Flow Chart for Baxalta 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)	On-Treatment BAL (Week 12-14)[b]	Week 13 (± 2 Days)	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[e]							
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)	On-Treatment BAL (Week 12-14)[b]	Week 13 (± 2 Days)	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination[c]
[redacted]			X[g]	X[g]		X[g]	X[g]	X[g]	
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				
[redacted]		X			X				

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

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[a] For subjects who undergo bronchoscopy/BAL procedures (see Section 10.3.4 for more details). 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 (see Section 10.3.4 for more details). The on-treatment bronchoscopy/BAL visit will be postponed once if a subject experiences a moderate or severe COPD exacerbation and/or LRTI (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 at 30 (± 15) 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 [FEV_1] and forced vital capacity [FVC]), which is to be taken 30 ± 15 minutes after administration of a short-acting inhaled β2 agonist bronchodilator (eg, 400 µg of salbutamol, or its equivalent).

[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.

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

[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.

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)	On-Treatment BAL (Week 12-14)[b]	Week 13 (± 2 Days)	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[e]			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)	On-Treatment BAL (Week 12-14)[b]	Week 13 (± 2 Days)	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[e]	P[e]		P[e]	P[e]	P[e]	P
[redacted]			P[e]	P[e]		P[e]	P[e]	P[e]	
Serum Anti-A1PI Antibodies[1]			S[e]			S[e]		S[e]	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]				
[redacted]		P[m]			P[m]				
BAL Urea[1]		L			L				
BAL Antigenic A1PI[1]		L			L				
BAL Functional A1PI (ANEC)[1]		L			L				
[redacted]		L			L				
[redacted]		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)	On-Treatment BAL (Week 12-14)[b]	Week 13 (± 2 Days)	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination[c]
[redacted]		L			L				
[redacted]		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 (see Section 10.3.4 for more details). 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 (see Section 10.3.4 for more details). The on-treatment bronchoscopy/BAL visit will be postponed once if a subject experiences a moderate or severe COPD exacerbation and/or LRTI (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] 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.

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[g] Complement activation and immune complex panel will consist of serum C3, C4, total complement (CH50), C1q binding, and circulating immune complexes.

[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, nitrite, 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 (≥11 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

Laboratory Test	Lowest Alert Limit	Highest Alert Limit	Comment
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		
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.

21. REFERENCE LIST

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22. SUMMARY OF CHANGES

Protocol Amendment 2: 2015 MAY 07
Replaces: Protocol Amendment 1: 2015 JAN 19

In this section, changes from the previous version of the Protocol Amendment 1, dated 2015 JAN 19, 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 was changed from Phase 4 to Phase 3/4.
   Purpose for Change: As the products do not have a market authorization in all of the target study countries, the clinical study phase was revised to include the pre-market authorization study phase (e.g. Phase 3/4).

3. **Throughout the document**
   Description of Change: (1) study sponsor was changed from Baxter Healthcare Corporation ("Baxter") to Baxalta US Inc. ("Baxalta"). (2) Baxter Innovations GmbH was removed from the list of study sponsors.
   Purpose for Change: (1) As the company Baxalta moves towards becoming a separate entity on July 1st, 2015, the name of the study sponsor has been revised accordingly. (2) Since last version of the protocol, the target country list has been finalized to US, Canada, and Australia which are all covered under the legal entity of Baxalta US Inc.

4. **Throughout the document**
   Description of Change: All references to the number of evaluable BAL subjects was changed from "at least 15" to "15 to 18".
   Purpose for Change: This change was made for consistency since both were previously written interchangeably throughout the protocol.

5. **Section 8.5 Randomization and Blinding**
   Description of Change: Revised the language regarding study personnel to remove reference to an unblinded pharmacist and study monitor(s).
   Purpose for Change: To reflect the plans for study conduct where blinding (of the GLASSIA lots) will be maintained via code IDs assigned, thus eliminating the need for unblinded study personnel.

6. **Section 3 Synopsis, Section 9.1 Inclusion Criteria #1**
   Description of Change: The age criteria were revised to include an upper age limit of 65 years for subjects who will be undergoing bronchoscopy/BAL procedures.
   Purpose for Change: Based on feedback obtained from a clinical expert, bronchoscopy/BAL procedures performed on individuals older than 65 years of age are associated with poorer returns even when the subject's FEV_1 is greater than 50%. The protocol was revised to specify subjects participating in the bronchoscopy/BAL component of the study must not exceed 65 years of age. Once the target number of BAL evaluable subjects has been reached, the upper age limit will not apply.

7. **Section 3 Synopsis, Section 9.1 Inclusion Criteria #2, Section 10.3.1.1 Confirmation of Severe Congenital A1PI Deficiency**
   Description of Change: The eligibility criteria was revised to state: "A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, Pi*Null/Null, **or other "at-risk" allelic combinations (excluding MS, MZ, and SZ).**"
   Purpose for Change: Based on feedback obtained from multiple clinical experts, the protocol was revised to expand the list of eligible A1PI genotypes that are associated with severe A1PI deficiency.

8. **Section 3 Synopsis, Section 9.1 Inclusion Criteria #3**
   Description of Change: The screening A1PI threshold was revised to be less than 11 µM, as follows: "Endogenous plasma (antigenic) A1PI level of <11 µM (A1PI measurement may be repeated for subjects with an initial screening A1PI level of 11 µM or above that is suspected to be due to inadequate washout of prior A1PI therapy)."

Purpose for Change: The screening A1PI level was revised based on feedback obtained from clinical experts/investigators, and for consistency with that used in the Kamada's pivotal efficacy study for GLASSIA as well as all other past and ongoing clinical trials evaluating the effects of A1PI augmentation therapy in patients with A1PI deficiency.

9. **Section 3 Synopsis, Section 9.1 Inclusion Criteria #4**
   Description of Change: The eligibility criteria was revised as follows: "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."
   Purpose for Change: To remove the phrase "within 52 weeks of screening" as this is not applicable.

10. **Section 3 Synopsis, Section 9.1 Inclusion Criteria #9 (b), Section 10.3.1.2.2 Single-Breath Determination of Carbon Monoxide Update in the Lung (DL_{CO})**
    Description of Change: Language regarding DLco was removed.
    Purpose for Change: To simplify screening procedures.

11. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #1**
    Description of Change: The eligibility requirement was reworded to state: "The subject is experiencing or has a history of clinically significant pulmonary disease (other than COPD, emphysema, chronic bronchitis, mild bronchiectasis, and stable asthma)."
    Purpose for Change: The language was reworded to provide clarity, and to explicitly state that subjects with stable asthma are not excluded from the study.

12. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #3**
    Description of Change: The eligibility requirement was revised to state: The subject routinely produces more than one tablespoon of sputum per day.
    Purpose for Change: Based on investigator feedback, the eligibility requirement was revised to specify the amount in tablespoons rather than milliliters as subjects may find this easier to measure and provide information to assess their eligibility.

13. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #4**
Description of Change: The eligibility requirement was revised to state: "4. The subject has a history of frequent pulmonary exacerbations (greater than 2 moderate or severe exacerbations within 52 weeks prior to screening; **see Section 10.4 for the definition of moderate and severe exacerbations**.)"
Purpose for Change: Based on investigator feedback, the reference to the definition of exacerbation severity was added to improve clarity.

14. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #6**
Description of Change: The eligibility requirement was revised as follows: "The subject has clinically significant abnormalities (other than emphysema, chronic bronchitis, or mild bronchiectasis) detected on chest X-ray or CT scan at the time of screening. (Past records obtained within 52 weeks prior to screening may be used, if available.)"
Purpose for Change: Based on investigator feedback, the eligibility requirement was revised to specify that subjects with mild bronchiectasis will not be excluded as bronchiectasis is common in this patient population.

15. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #7**
Description of Change: The eligibility requirement was moved from inclusion criteria section to exclusion criteria section: "The subject has clinically significant abnormalities detected on a 12-lead electrocardiogram (ECG) performed at the time of screening. (Past records obtained within 26 weeks prior to screening may be used, if available.)"
Purpose for Change: To improve readability.

16. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #11**
Description of Change: The eligibility requirement was revised as follows: "The subject is receiving long-term **around-the-clock** oxygen supplementation. (**The following are allowed: short-term use of oxygen supplementation [eg, for the management of acute COPD exacerbation], oxygen supplementation required during night time only, and** supplemental O_2 with continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]).
Purpose for Change: Based on investigator feedback, the eligibility requirement was revised to clarify that only long term around-the-clock oxygen supplementation is not allowed. This patient population quite commonly uses oxygen supplementation at night time or on a short-term basis (eg, for pulmonary exacerbation).

17. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #15**
Description of Change: The following eligibility requirement was revised as follows: "**Ongoing active infection with** hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection **at the time of screening**."
Purpose for Change: Based on investigator feedback, the eligibility requirement was revised to specify that subjects with ongoing active infection of these viruses at the time of screening will be excluded from the study. Subjects with positive serology results (eg, hepatitis B) due to past infection or vaccination will be allowed.

18. **Section 3 Synopsis, Section 9.2 Exclusion Criteria #20**
Description of Change: The eligibility requirement was revised to state: "The subject has contraindication(s) to bronchoscopy such as recent myocardial infarction, unstable angina, other cardiopulmonary instability, tracheal obstruction or stenosis, moderate to severe hypoxemia or any degree of hypercapnia, unstable asthma, Stage 4 or 5 chronic kidney disease, pulmonary hypertension, severe hemorrhagic diathesis, and cervical C1/C2 arthritis."
Purpose for Change: To more accurately define the medical terms that may predispose subjects to risks associated with bronchoscopy procedures.

19. **Section 9.3 Withdrawal and Discontinuation, Section 10.3.1 Screening Visit**
Description of Change: The following text (in bold font) "For subjects undergoing BAL procedures, if no acceptable 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. **These subjects may be re-screened after the target enrollment of BAL evaluable subjects is completed**." and "**Subjects who were discontinued early from the study due to failure to yield adequate baseline BAL samples will be allowed to rescreen after the target enrollment of BAL evaluable subjects is completed**." were added.
Purpose for Change: To clarify that subjects who failed baseline BAL visit will be allowed to rescreen but only when the BAL target has been reached and enrollment is still open to fulfill a minimum of overall 36 randomized subjects.

20. **Section 10.3.2.1 IP Administration, Section 12.10 Vital Signs, Table 20.2-1 Schedule of Study Procedures and Assessments**
Description of Change: The window for obtaining vital signs was changed from "~~within 90 minutes~~" to "**at 30 (± 15) minutes**" after the completion of an infusion.
Purpose for Change: The post-infusion vital sign collection time point was revised to allow flexibility of 15 minutes, while standardizing within a tighter timeframe of 30 minutes rather than 90 minutes.

21. **Section 3 Synopsis, Section 10.3.4 BAL Visit, Supplement 20.5 Bronchoscopy/Bronchoalveolar Lavage Procedure (in previous protocol versions)**
Description of Change: The description of an acceptable BAL sample from the baseline and on-treatment BAL visit was defined as total recovery of ≥20% of the instilled volume of saline.
Purpose for Change: The acceptance criteria for BAL was simplified based on feedback received from clinical expert. Details of the bronchoscopy/BAL procedures (previously in Supplement 20.5) were deleted from the protocol as guidance/instructions will be detailed in the bronchoscopy/BAL manual to be provided to study sites.

22. **Section 10.3.4 BAL Visit**
Description of Change: The following text were added: "**The baseline bronchoscopy/BAL visit must be completed prior to randomization and within 48 hours prior to the first IP administration**." and "**The on-treatment bronchoscopy/BAL procedure will be conducted 7 (± 1) days following the last IP infusion, but must be completed prior to the next IP infusion. Whenever possible, it is recommended that sufficient time (typically 24 to 48 hours) is allowed for the subject to recover from the bronchoscopy/BAL procedure**."
Purpose for Change: To revise and clarify the timing of bronchoscopy/BAL procedures relative to randomization and IP infusions, based on feedback from clinical expert.

23. **Section 11.2** [redacted]

24. **Section 12.7.4 Urine Tests, Section 20.3 Schedule of Clinical Laboratory Assessments**

Description of Change: Urinalysis panel will include nitrite, rather than nitrate.

Purpose for Change: To correct for the appropriate analyte.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: GLASSIA

STUDY TITLE: A Phase 3/4 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

PROTOCOL IDENTIFIER: 471101

CLINICAL TRIAL PHASE 3/4

AMENDMENT 2: 2015 MAY 07
Replaces Amendment 1: 2015 JAN 19

ALL VERSIONS:
Amendment 2: 2015 MAY 07
Amendment 1: 2015 JAN 19
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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