PROTOCOL: 471101

TITLE:	A Phase 3/4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha1-Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects
SHORT TITLE:	Ph 3/4 GLASSIA Safety, Immunogenicity, and Bronchoalveolar Lavage Study
STUDY PHASE:	Phase 3/4
DRUG:	GLASSIA
NCT NUMBER:	NCT02525861
IND NUMBER:	14774
SPONSOR:	**Baxalta US Inc.***, 300 Shire Way, Lexington, MA 02421, USA AND **Baxalta Innovations GmbH***, Industriestrasse 67, A-1221 Vienna, Austria * Baxalta is now part of Shire
PROTOCOL HISTORY:	**AMENDMENT 7: 2020 MAY 26** **Replaces: Amendment 6: 2018 AUG 27** **ALL VERSIONS:** Amendment 7: 2020 MAY 26 Amendment 6: 2018 AUG 27 Amendment 5: 2017 NOV 21 Amendment 4: 2016 JAN 15 Amendment 3: 2015 AUG 26 Amendment 2: 2015 MAY 07 Amendment 1: 2015 JAN 19 Original: 2011 JUL 05

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted] **Date:** [redacted]

[redacted] MD [redacted]

Investigator's Acknowledgement

I have read this protocol for Study 471101.

Title: A Phase 3/4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha1-Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____
Signature:	**Date:**
_____	_____

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

[redacted], MD

[redacted]

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, INCLUDING SUSARs, 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.

Drug Safety contact information: see SAE Report Form.
Refer to SAE Protocol Sections and the study team roster for further information.

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

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- 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	Q4 2015
Primary Completion	Q3 2020
Study Completion	Q1 2021
Duration	Approximately 5 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of the study is 2-fold: (1) to further evaluate the safety and potential immunogenicity of GLASSIA following intravenous (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 IV administration at a dosage of 60 mg/kg body weight (BW)/week active A1PI protein 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 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 is a 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 active A1PI protein (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. A subject will be considered evaluable only if acceptable BAL samples (see Section 10.3.4 for definitions) are obtained at both baseline and on-treatment BAL visits. Once the target of 15 to 18 evaluable subjects has been reached, the remaining subjects to be enrolled will not be required to undergo baseline and on-treatment bronchoscopy/BAL procedures. Subjects with confirmed medical history (IC #1a, #9a, #9b, ExC #20, #21, #22, #23, and #24) known not to meet eligibility criteria to undergo bronchoscopy/BAL procedures, may be screened and randomized with sponsor approval before the target enrollment of BAL evaluable subjects is reached. 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 last A1PI treatment) during screening. Screening A1PI measurement may be taken at any time during the screening period for treatment-naïve

subjects. For subjects who have previously received alpha-1 augmentation therapy however, screening A1PI measurement should be taken after the washout period. 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 approved labeled dosage of 60 mg/kg BW/week active A1PI protein 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 1 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 active A1PI protein 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 7, Week 13, Week 19, 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 BW 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 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 (particle load) 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 (thresholds as outlined in Section 20.4) 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 active A1PI protein **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 75 years of age at the time of screening.
   (b) For subjects who will be waived from undergoing bronchoscopy/BAL procedures -: 18 years of age or older at the time of screening.

2. Documented A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, Pi*Null/Null, or other "at-risk" allelic combinations such as SZ (excluding MS and MZ without the presence of another allowable at-risk genotype) and an endogenous A1PI plasma levels of ≤11 µM (≤0.572 mg/mL).
3. Screening levels of endogenous plasma (antigenic) A1PI of ≤11 µM at any time during the screening period for treatment-naïve subjects, or following a 4-week minimum washout from previous augmentation therapy in treatment-experienced subjects.
4. Subjects must have at least one of the following: clinical diagnosis of emphysema, evidence of emphysema on chest X-ray or 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. Subjects with a positive cotinine test due to nicotine replacement therapy (eg, patches, chewing gum), vapor cigarettes, or snuff are eligible.
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 function at the time of screening which meets both of the following:
   (a) Post-bronchodilator forced expiratory volume in 1 second (FEV1) ≥50% of predicted
   (b) If FEV1 is >80% predicted, then FEV1/forced vital capacity (FVC) must be <0.7.

Note: Inclusion criterion #1a, #9a, and #9b are not applicable to subjects who are 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 chronic severe cor pulmonale (resting mean pulmonary artery pressure ≥40 mm Hg).
3. The subject routinely produces more than 1 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 rescreened 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 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 (O_2) supplementation. (the following are allowed: short-term use of O_2 supplementation [eg, for the management of acute COPD exacerbation], O_2 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 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 IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP 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.

Note: Exclusion criteria #20, #21, #22, #23, and #24 are not applicable to subjects who are not required to undergo the bronchoscopy/BAL procedures.

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.

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 1-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 1-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 will be summarized in the following subgroups: by sex, age (≤65; >65), race, and ethnicity.

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 treatment-emergent immunogenicity, any potential temporal relationship of anti-A1PI antibody formation with the occurrence of potentially immune-mediated AEs will be examined.

Summary tables of laboratory data as well as shift tables of normal versus abnormal low / high laboratory values will be created by each treatment arm as well as pooled together. In addition, shift tables of normal versus abnormal clinically significant / not-clinically significant laboratory values (using thresholds in section 20.4) will be created separately by each treatment arm as well as pooled together. The clinical significance of abnormal laboratory values as assessed by the investigator is to be captured in the source documents. Abnormal laboratory values considered clinically significant by the investigator are to be reported in the CRF as an AE or as Medical History (depending on whether they occurred during or after the first infusion or prior to the first infusion).

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

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
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
ANOVA	Analysis of Variance
APE	Acute pulmonary exacerbation
AR/ARs	Adverse reaction/adverse reactions
AST	Aspartate aminotransferase
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
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF(s)	Case report form(s)
CT	Computerized tomography
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram

Abbreviation	Definition
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
ELF	Epithelial lining fluid
EP	European Pharmacopeia
ExC	Exclusion criterion
FAS	Full analysis set
FDA	United States Food and Drug Administration
FEV_1	Forced expiratory volume in 1 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
IC	Inclusion criterion
ICF	Informed consent form
ICH	International Council for Harmonisation
IgA	Immunoglobulin A
IP	Investigational product
IRT	Interactive response technology
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactic dehydrogenase
LRT	Lower respiratory tract

Abbreviation	Definition
LRTI	Lower respiratory tract infection
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
NAT	Nucleic acid test
NE	Neutrophil elastase
NMC	Non-medical complaint
NYHA	New York Heart Association
O_2	Oxygen
PCR	Polymerase chain reaction
PP	Per-protocol
RBC	Red blood cell
RSI	Reference safety information
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, the 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 A1PI. GLASSIA A1PI functional activity is independent of the particulate load of the solution for infusion. Protein aggregation is a known phenomenon with protein therapeutics and has been shown to be present in the active comparator used in the Phase 2/3 trial, as well as in 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 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 1 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. GLASSIA lots with at least a factor of 2-fold differential 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 raised about protein aggregates in a therapeutic product regarding the potential safety risks to humans. To address these concerns, a key goal of this study is to evaluate the clinical safety profile of GLASSIA with a 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 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 through 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 (IV infusion), as well as the infusion rate (maximum 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 2 single dose general toxicology studies in Sprague-Dawley rats and New Zealand White rabbits, and 2 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 BW, clinical chemistry, hematology and gross pathology that could be attributed to GLASSIA administration.

In a repeated dose study, New Zealand White rabbits received GLASSIA (300 mg/kg) once daily for 5 consecutive days. Animals were monitored for changes in clinical signs, BW, 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 2 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 Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP E6(R2), November 2016), Title 21 of the US Code of Federal Regulations (US CFR), the (EU Directives 2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is 2-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 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 last A1PI treatment) during screening. Screening A1PI measurement may be taken at any time during the screening period for treatment-naïve subjects. For subjects who have previously received alpha-1 augmentation therapy, screening A1PI measurement should be taken at the end of the washout period. 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 not be required to undergo baseline and on-treatment bronchoscopy/BAL procedures. Subjects with confirmed medical history (IC #1a, #9a, #9b, ExC #20, #21, #22, #23, and #24) known not to meet eligibility criteria to undergo bronchoscopy/BAL procedures, may be screened and randomized with sponsor approval before the target enrollment of BAL evaluable subjects is reached.

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 achieved with initial 36 randomized subjects, additional subjects will be enrolled to meet 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 1 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 7, Week 13, Week 19, 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 BW measurements, as well as physical examination, vital sign measurements, and blood draws 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 and [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 5 years from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit).

The recruitment period is expected to be approximately 46 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 particle load 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 (thresholds as outlined in Section 20.4) 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. This study will include a Data Monitoring Committee (DMC) to monitor the study for any safety or medical concerns, and may recommend stopping the study based on the criteria defined in the DMC charter (see Section 16.4).

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

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 BW at screening and at each subsequent study visit. Dose adjustments based on BW changes from screening or previous visit will be made if the subject's BW changes by >5%. Only BW 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 IV use only.

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

Rate of administration: maximum rate of 0.2 mL/kg BW/min
(The rate of infusion may be regulated by an ambulatory infusion pump, if available, not exceeding an infusion rate of 0.2 mL/kg BW/min.)

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.

No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and 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 75 years of age at the time of screening.
   (b) For subjects who will be waived from undergoing bronchoscopy/BAL procedures: 18 years of age or older at the time of screening.
2. Documented A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, Pi*Null/Null, or other "at-risk" allelic combinations such as SZ (excluding MS and MZ without the presence of another allowable at-risk genotype) and an endogenous A1PI plasma levels of ≤11 µM (≤ 0.572 mg/mL).
3. Screening levels of endogenous plasma (antigenic) A1PI of ≤11 µM may be collected at any time during the screening period for treatment-naïve subjects, or following a 4 week minimum washout from previous augmentation therapy in treatment-experienced subjects.
4. Subjects 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. Subjects with a positive cotinine test due to nicotine replacement therapy (eg, patches, chewing gum), vapor cigarettes, or snuff are eligible.
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 function 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 #1a, #9a, and #9b are not applicable to subjects who are 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 chronic severe cor pulmonale (resting mean pulmonary artery pressure ≥40 mm Hg).
3. The subject routinely produces more than 1 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 rescreened 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 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 (O2) supplementation. (The following are allowed: short-term use of O2 supplementation [eg, for the management of acute COPD exacerbation], O2 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 HAV, HBV, hepatitis C virus (HCV), or 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 IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP 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.

Note: Exclusion criteria #20, #21, #22, #23, and #24 are not applicable to subjects who are not required to undergo the bronchoscopy/BAL procedures.

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.

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 IP/device other than IP.
5. If a subject experiences >1 moderate or severe COPD exacerbation and/or lower respiratory tract infection (LRTI) during the screening period (Rescreening may be permitted as defined in Section 10.3.1.3).
6. 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 screen failed and then rescreened based solely on this reason. The subject may be randomized to the immunogenicity portion of the study without the need to rescreen, with sponsor approval, provided they are within the screening window and meet all applicable criteria. 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 SIC: protocol identifier (eg, 471101) to be provided by the sponsor, 3-digit number study site number (eg, 002) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of enrollment (ie, signing the ICF). For example, the third subject who signed an ICF at study site 002 will be identified as Subject 471101-002003. 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, 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) and screening assessments (see Section 20.2 and Section 20.3 for detailed list of study procedures/laboratory assessments including serum IgA, ECG, and Chest X-ray/CT). 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 who provided informed consent. 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. If a subject is rescreened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

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 by measurement of endogenous plasma A1PI levels. The plasma level must be ≤11 µM, and the plasma sample can be collected any time during screening for treatment-naïve A1PI deficient subjects, but only following a washout from previous A1PI augmentation therapy in treatment-experienced subjects. The presence of exogenously-administered A1PI may interfere with the verification of endogenous plasma A1PI levels in treatment-experienced subjects; therefore, they will be required to have their pre-study A1PI therapy withdrawn for a minimum of 4 weeks to allow A1PI levels to return to the subject's pre-augmentation levels. Screening A1PI measurement may be repeated in the event of suspected inadequate washout resulting in initial screening A1PI level of >11 µM.

Subjects must have a diagnosis of A1PI deficiency (ie, genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, or Pi*Null/Null, or other "at-risk" allelic combinations such as SZ [excluding MS and MZ without the presence of another allowable at-risk genotype]) AND plasma antigenic A1PI level of ≤11 µM in order to meet eligibility criteria. Results of these screening tests will be used to establish the subject's eligibility for participation in the study.

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 × 200 µg or 4 × 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 rescreened 4 weeks after the clinical resolution of an exacerbation).
4. Ineligibility due to failure to meet protocol pre-specified time intervals (eg, inclusion criteria #5 and #6, and exclusion criteria #5 and #17).
5. For additional reasons after discussion with the medical monitor and sponsor approval.

Subjects who were discontinued early from the study due to failure to yield adequate baseline BAL samples or failure to meet the eligibility criteria required to undergo the bronchoscopy/BAL procedure will be allowed to be rescreened before the target enrollment of BAL evaluable subjects is completed.

If a subject is to be rescreened, 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.

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). If a weekly infusion is more than +5 days from the expected date, the infusion should be skipped and the next regularly scheduled infusion should take place.

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 in Section 8.7.

The first infusion (Week 1), as well as infusions during Week 7, Week 13, Week 19, 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°C (101°F)

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

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

10.3.2.2 Management of Treatment-Emergent (S)AEs

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

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

In the event of a life-threatening SAE, study personnel should take immediate steps to preserve the subject's well-being and call for emergency assistance, as well as contact the investigator 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 rechallenge 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 will take place at study site 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 at least 1 acceptable BAL sample obtained from any of the 3 lobes from each visit and meeting the following criteria:
  - total recovery of ≥20% of the instilled volume of saline per lobe, and
  - BAL sample shows no blood by visual inspection.

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 (≤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 (as per criteria above). 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 screen failed and then rescreened based solely on this reason.

The subject may be randomized to the immunogenicity portion of the study without the need to rescreen, with sponsor approval, provided they are within the screening window and meet all applicable criteria.

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.

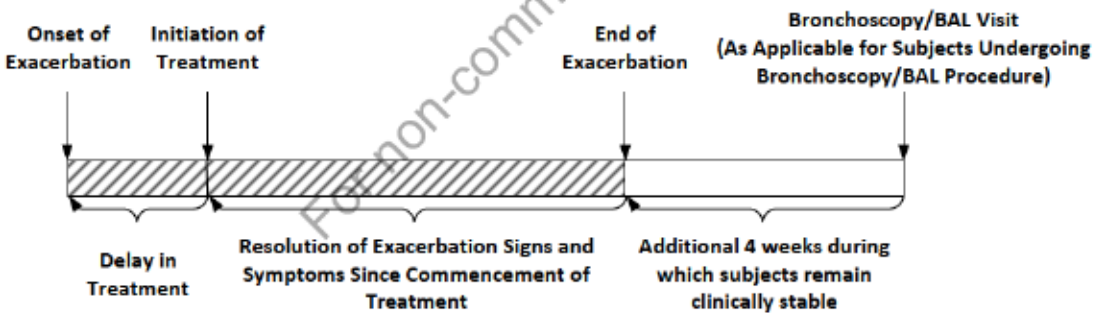
In order to assess the effects of GLASSIA maintenance treatment on the ELF A1PI levels, it is important for the on-treatment BAL procedure be performed after stable dosing of GLASSIA has been maintained for at least 4 half-lives of A1PI (ie, average half-life ~4.6 days, see GLASSIA package insert and/or 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

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 IV) 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, (S)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]

[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

An SAE is defined as an untoward medical occurrence that at any dose meets 1 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 B19V.

12.1.1.1.1 Uncomplicated Pregnancies

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 AE which met any of the following criteria:

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

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

(c) an AE 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 AE that began during infusion or within 24 hours following the end of IP infusion, or

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

(c) an AE 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 (RSI) (eg, IB, package insert). "Unexpected" also refers to the AEs that are mentioned in the RSI as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. The expectedness of AEs will be determined by the sponsor using the IB and/or prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

12.1.1.5 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 within 24 hours of awareness and followed-up at estimated date of delivery and 1 year post-delivery, if feasible. (S)AEs associated with these events must be reported on the appropriate (S)AE forms, and follow the guidance on timing of the report provided in Section 12.1.2.3.

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 (from first IP exposure) 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 IP, 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 CRF (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 backup 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 backup paper SAE Report Form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or backup 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)
- IP 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 (ie, action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (ie, 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 (EC) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

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: 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.

Whole blood will be collected for the assessment of hematology and serum for 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.

12.7.1.1 Other Analysis

Serum samples will be collected for serum cotinine concentrations for nonsmoking assessments (levels within normal range of a nonsmoker).

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 assay for 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

At screening, subjects would be tested for HAV, Hep B, HCV and HIV1/HIV2 by serology for antigenemia or antibodies or by PCR based NAT, towards 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 (1 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 (1 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 1 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-mediated AEs. 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 (mm Hg). 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 ≥38.2ºC (101ºF).

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 1-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 1 IP infusion and have at least 1 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 which may impact the efficacy assessment. 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 2 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 1 evaluable sample per BAL visit with no missing infusion(s) within 4 weeks immediately preceding the on-treatment BAL procedure.
- Subjects must have acceptable ELF data (definition as per Section 10.3.4) 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 Per-Protocol BAL Analysis Set

The per-protocol BAL (PPBAL) analysis set will be a subset of the BAL analysis set with no major protocol deviations that may impact the BAL assessment. Further details will be given in the statistical analysis plan.

13.2.5 Safety Analysis Set

The safety analysis set will include all subjects enrolled in the study who received at least 1 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.

Since an increase from baseline in the mean ELF levels of antigenic A1PI is expected, a 1-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:

H_0: Mean change in antigenic A1PI in the ELF from baseline to the on-treatment measurement will be less than or equal to zero.

$$H_0: \mu_d \leq 0$$

H_1: Mean change in antigenic A1PI in the ELF from baseline to the on-treatment measurement will be greater than zero.

$$H_1: \mu_d > 0$$

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

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 separately by treatment arm as well as pooled across both treatment arms for the FAS and PP analysis sets. 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 for the BAL and PPBAL analysis sets.

In the event that 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 and 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.

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-mediated AEs, if any, will be examined.

Summary tables of laboratory data as well as shift tables of normal versus abnormal low / high laboratory values will be created by each treatment arm as well as pooled together. In addition, shift tables of normal versus abnormal clinically significant / not-clinically significant laboratory values (using thresholds in section 20.4) will be created separately by each treatment arm as well as pooled together. The clinical significance of abnormal laboratory values as assessed by the investigator is to be captured in the source documents and is to be reported in the CRF as follows:

- Abnormal laboratory values that are considered clinically significant by the investigator and occurred prior to the first infusion will be reported as medical history.
- Abnormal laboratory values that are considered clinically significant by the investigator and occurred during or after the first infusion will be reported as an AE.

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.

15.3.1 Safety Monitoring

The safety of the subjects in this study shall be monitored by an external Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of pulmonary clinical care and research who are not recruiting subjects for this study.

The DMC will recommend to the sponsor whether to continue or stop the trial or to continue the study after proper amendment to the protocol.

15.4 Auditing

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

This study will be monitored by Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of A1PI deficiency and COPD clinical care and research who are not recruiting subjects for this study.

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

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

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

17.2 Study 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.

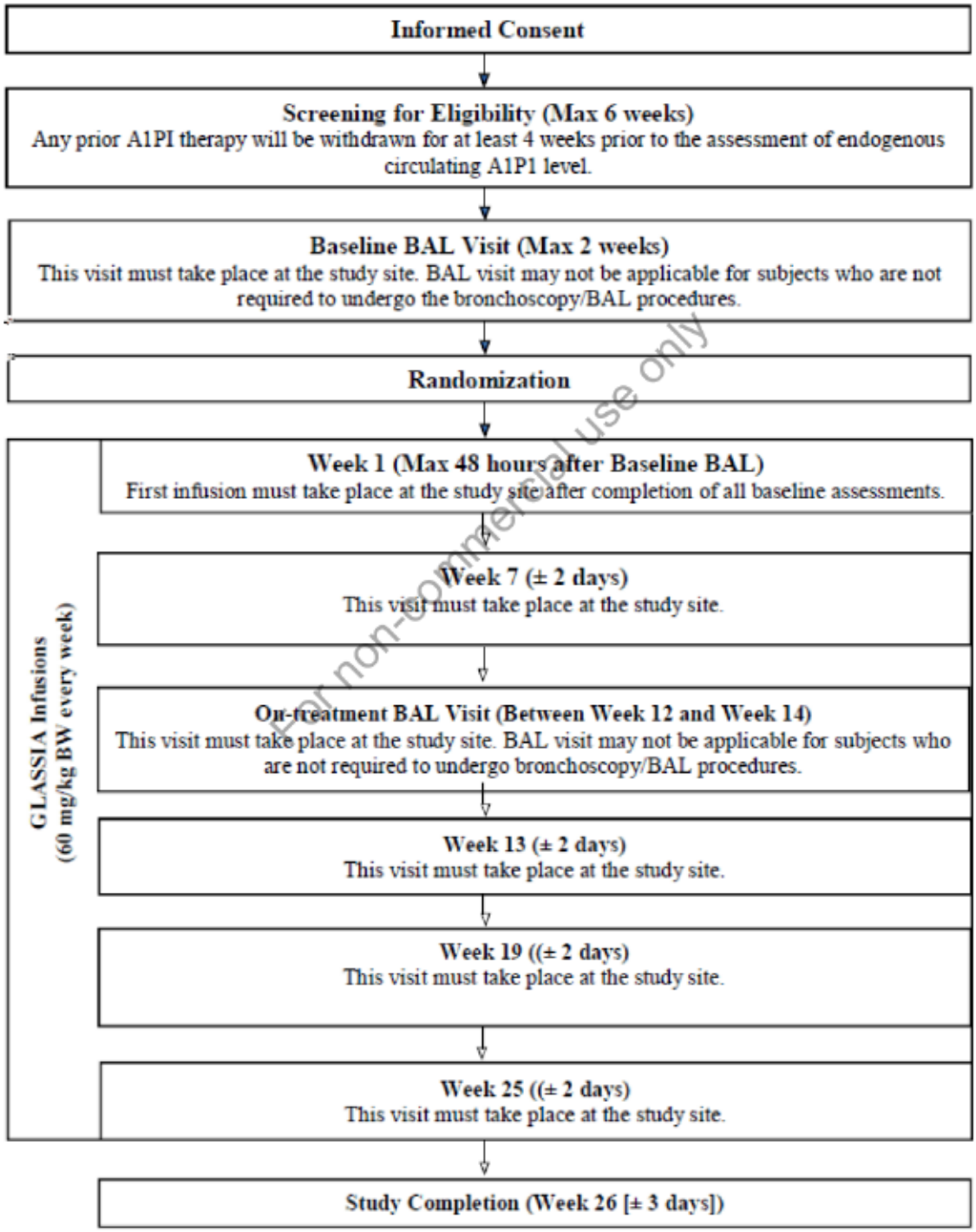
19. PUBLICATION POLICY

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 (Max 48 hours after Baseline BAL)	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[g]	X[g]	X[g]	
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
[redacted]			X[g]	X[g]		X[g]	X[g]	X[g]	

Table 20.2-1
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening (Max 6 Weeks)	Baseline BAL[a] (Max 2 Weeks)	Week 1 (Max 48 hours after Baseline BAL)	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]
Anti-A1PI Antibodies[m,n]			X[g]			X[g]		X[g]	X
Weekly GLASSIA Infusions[o]			X →	→	→	→	→	→	
Adverse Event		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				

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

[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.

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[d] Written informed consent must be obtained prior to performance of any study procedures including screening/rescreening 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). Bronchoscopy/BAL visit with evaluable BAL samples collected must be completed prior to randomization and within 48 hours prior to the first IP administration.

[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. Dose adjustment based on body weight changes during the course of the study may be made if the changes are clinically significant (eg, >5%).

[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]) to be performed in triplicate, which is to be taken 30±5 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.

[n] In the event of suspected immune-related AEs, 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 7, Week 13, Week 19, 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 AEs 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 (Max 48 hours after Baseline BAL)	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, HBV, HCV, and HIV1/HIV2 by serology for antigenemia or antibodies or by PCR based NAT	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	
Screening (Antigenic) A1PI[k,l]	P								
On-Treatment Trough Plasma Antigenic A1PI[l]			P[e]	P[e]		P[e]	P[e]	P[e]	P
On-Treatment Trough Plasma Functional 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 (Max 48 hours after Baseline BAL)	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]			P[e]	P[e]		P[e]	P[e]	P[e]	
Serum Anti-A1PI Antibodies[l]			S[e]			S[e]		S[e]	S
Additional Procedures for Subjects Undergoing BAL Procedures									
Plasma Urea[l]		P[m]			P[m]				
Plasma Antigenic A1PI[l]		P[m,n]			P[m]				
Plasma Functional A1PI[l]		P[m]			P[m]				
[redacted]		P[m]			P[m]				
BAL Urea[l]		L			L				
BAL Antigenic A1PI[l]		L			L				
BAL Functional A1PI (ANEC)[l]		L			L				
[redacted]		L			L				
[redacted]		L			L				
[redacted]		L			L				

Abbreviations: BAL = Bronchoalveolar lavage; W = Whole blood; S = Serum; HAV = Hepatitis A Virus; HBV = Hepatitis B virus; 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]

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[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: Hgb, hematocrit (Hct), erythrocytes (ie, red blood cell [RBC]) count, leukocytes (ie, white blood cell [WBC]) count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), absolute neutrophil count (ANC), absolute lymphocyte count, reticulocyte count, and platelet count.

[e] Samples must be collected prior to GLASSIA administration.

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

[g] Complement activation and immune complex panel will consist of serum C3, C4, 50% hemolytic complement activity of serum (CH50), C1q binding assay (circulating immune complexes).

[h] Viral testing will consist of viral serology for 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. 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.

[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. The clinical significance of abnormal laboratory values is to be captured in the source documents. Abnormal laboratory values considered clinically significant by the investigator are to be reported in the CRF as an AE or as Medical History, depending on whether they occurred during or after the first infusion or prior to the first infusion. 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			
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

Laboratory Test	Lowest Alert Limit	Highest Alert Limit	Comment
Serum albumin	<3.0 g/dL	----	May indicate protein loss, inflammation or malnutrition
Complement Activation and Immune Complex			
Serum C3	<70 mg/dL	---	
Serum C4	<14 mg/dL	---	
Total complement (CH50)	<30 U/ml	---	
C1q binding/CICs	<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.

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22. SUMMARY OF CHANGES

Protocol Amendment 7: 2020 MAY 26

Replaces: Protocol Amendment 6: 2018 AUG 27

In this section, changes from the previous version of the Protocol Amendment 6, dated 2018 AUG 27, 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.
   Purpose of Change: To improve the readability and/or clarity of the protocol, and to reflect minor administrative/operational changes.

2. **Section 6.1.2 and Section 8.7.3 (Product administration)**
   Description of Change: The rate of administration was clarified as follows: **"maximum rate** of 0.2 mL/kg BW/min (The rate of infusion **may** be regulated by an ambulatory infusion pump, **if available, not exceeding an infusion rate of 0.2 mL/kg BW/min.)**"
   Purpose of Change: To clarify that subjects may receive a slower infusion rate. The rate of administration should be a maximum rate of 0.2 mL/kg BW/min in accordance with the Package Insert for GLASSIA.

3. **Synopsis and Section 8.3 (Planned Study Period)**
   Description of Change: The primary completion was updated to Q3 2020 and study completion updated to Q1 2021. The overall duration of the study will be approximately 5 years from study initiation. The recruitment period is now expected to be approximately 46 months.
   Purpose of Change: Update of study duration and timelines.

4. **Synopsis and Section 8.4.2 (Secondary Outcome Measures)**
   Description of Change: The secondary outcome measure description was clarified as follows (see added text in bold): "Number (proportion) of subjects who experienced a shift from normal or clinically insignificant abnormal laboratory values at baseline to clinically significant abnormal laboratory values **(thresholds as outlined in Section 20.4)** following GLASSIA administration."
   Purpose of Change: Clarification that thresholds for clinically significant laboratory abnormalities as outlined in Section 20.4 will be used for the shift analysis.

5. **Section 8.4.3 (Exploratory Outcome Measures)**
Description of Change: [redacted]

Purpose of Change: Section 8.4.3 revised as it had not been amended in line with proposed changes in the Study Synopsis during Protocol Amendment 3, dated 26 August 2016.

6. **Section 10.3.4 (BAL Visits)**
Description of Change: The text for acceptable BAL sample criteria was modified to read as follows:
"An evaluable subject is defined as a subject who:

- has successfully completed both the baseline and the on-treatment BAL visits, and
- has at least 1 acceptable BAL sample obtained from any of the 3 lobes from each visit and meeting the following criteria:
  - total recovery of ≥20% of the instilled volume of saline per lobe, and
  - BAL sample shows no blood by visual inspection

The following text was deleted "…, overall number of acceptable aliquots no less than 3 per lobe".

Purpose of Change: The text was modified for clarity and to be consistent with the study procedures. The deleted text was added in error in Protocol Amendment 4 and subsequent amendments. Standard procedures for obtaining BAL sample aliquots vary from site to site and no specific instructions on obtaining BAL sample aliquots were provided to the study sites; all remaining sample criteria were confirmed to be valid.

7. **Section 12.9, Section 13.4.3 and Table 20.2.1 (Immunogenicity)**
Description of Change: Change of wording from "immune-related" to "immune-mediated" treatment-emergent ARs in several sections.
Purpose of Change: Wording updated for consistency throughout the protocol.

8. **Section 13.2.2 (Per-Protocol Analysis Set)**
Description of Change: The text for subjects undergoing BAL procedures was modified as follows (see added text in bold): "The per-protocol (PP) analysis set will include a subset of the full analysis set, comprising subjects with no major protocol deviations **which may impact the efficacy assessment**. 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 2 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."
Purpose of Change: The text was modified to clarify that all major protocol deviations will be reviewed for their potential impact on efficacy assessments.

9. **Section 13.2.3 (BAL Analysis Set)**
Description of Change: The following text was updated to read: "Subjects must have **acceptable** ELF data **(definition as per Section 10.3.4)** 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."
Purpose of Change: To clarify that a definition for acceptable ELF data can be found in Section 10.3.4 which defines the criteria for acceptable BAL samples.

10. **Section 13.2.4 (Per-Protocol BAL Analysis Set)**
Description of Change: This is a newly added subsection. The following text was added: The per-protocol BAL analysis set will be a subset of the BAL analysis set with no major protocol deviations that may impact the BAL assessment. Further details will be given in the statistical analysis plan."
Purpose of Change: This analysis set was added to assess the impact of major protocol deviations on the BAL assessments.

11. **Section 13.4.1 (Efficacy Outcome Measures)**
Description of Change: The following text was added: "A sensitivity analysis will be performed based on the PPBAL analysis set."
Purpose of Change: Addition of a sensitivity analysis for the additional analysis set described in Section 13.2.4 (Per-Protocol BAL Analysis Set).

12. **Synopsis (Planned Statistical Analysis) and**
Section 13.4.1 (Efficacy Outcome Measures)
Description of Change: The following sentence was deleted: [redacted]
Purpose of Change: [redacted].

13. **Section 13.4.2 (Exposure Analysis)**
Description of Change: The text was revised as follows (see added text in bold and deleted text):
"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 **separately by treatment arm as well as** pooled across both treatment arms **for the FAS and PP analysis sets**. 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 **for the BAL and PPBAL analysis sets**. ~~Plasma A1PI levels obtained at the study completion (Week26) 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.~~**"**
Purpose of Change: The Early Termination and Completion visits will now be included in the summary tables. Additionally, it was clarified on which datasets the analyses will be done (in accordance with the Statistical Analysis Plan).

14. **Section 13.4.3 (Safety Outcome Measures)**
Description of Change: In the following text "or" was replaced by "and" to read :
"AEs that are considered potentially related to the presence of protein aggregates **and** 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."
Purpose of Change: The text was changed for clarity as the analysis will focus on the primary outcome measure for the study, ie, the "Number (proportion) of AEs considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution".

15. **Synopsis and Section 13.4.3 (Safety Outcome Measures)**
Description of Change: The following text related to safety outcome measures was deleted: "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."
Purpose of Change: The analysis was determined not to be required for the study due to the small sample size.

16. **Synopsis (Planned Statistical Analysis) and Section 13.4.3 (Safety Outcome Measures)**
Description of Change: The section was updated to clarify the following scheduled analysis of laboratory data:
"Summary tables of laboratory data as well as shift tables of normal versus abnormal low / high laboratory values will be created by each treatment arm as well as pooled together. In addition, shift tables of normal versus abnormal clinically significant / not-clinically significant laboratory values (using thresholds in Section 20.4) will be created separately by each treatment arm as well as pooled together. The clinical significance of abnormal laboratory values as assessed by the investigator is to be captured in the source documents and is to be reported in the CRF as follows:

- Abnormal laboratory values that are considered clinically significant by the investigator and occurred prior to the first infusion will be reported as medical history.
- Abnormal laboratory values that are considered clinically significant by the investigator and occurred during or after the first infusion will be reported as an AE.

The following text was deleted: "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."

Purpose of Change: Due to the sample size, it was determined that 95% CI would not be needed for the shift tables. The scheduled analysis of laboratory data was further clarified including how abnormal laboratory values are to be assessed and reported by the investigator.

17. **Section 20.4 (Thresholds for Clinically Significant Laboratory Abnormalities)**
Description of Change: The following text was added:
"The clinical significance of abnormal laboratory values is to be captured in the source documents. Abnormal laboratory values considered clinically significant by the investigator are to be reported in the CRF as an AE or as Medical History, depending on whether they occurred during or after the first infusion or prior to the first infusion."
Purpose of Change: Clarification that abnormal laboratory values are to be captured in the source documents and are to be reported in the CRF as AEs or as Medical History.