STATISTICAL ANALYSIS PLAN

NCT Number: NCT02525861

Study 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

Study Number: 471101

SAP Version and Date:

Version 1: 09 Sep 2020

STATISTICAL ANALYSIS PLAN

GLASSIA
PHASE 3/4

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

PROTOCOL IDENTIFIER: 471101

Study Sponsor(s): Baxalta US Inc.*
300 Shire Way, Lexington MA
02421, USA
* Baxalta is now part of Takeda

Baxalta Innovations GmbH*
Industriestrasse 67
A-1221 Vienna, AUSTRIA

Author: [redacted], [redacted], IQVIA

Protocol: 26May2020, Amendment 7

SAP Version #: Final v1.0

SAP Date: 09Sep2020

Status: Final

REVISION HISTORY

Version	Issue Date	Summary of Changes
Draft 1.0	09Apr2019	New Document
Draft 2.0	24May2019	Updated document based on sponsor review.
Final Draft 1.0	23Aug2019	Updated document based on sponsor review.
Final Draft 2.0	09Sep2019	Updated document based on sponsor review.
Final Draft 3.0	17Apr2020	Updated document based on sponsor review.
Final Draft 4.0	29Apr2020	Updated document based on sponsor review.
Final Draft 5.0	29May2020	Updated document based on sponsor review.
Final Draft 6.0	10Jun2020	Updated document based on sponsor review.
Final Draft 7.0	29Jun2020	Updated document based on sponsor review.
Final	09Sep2020	Updated document based on sponsor review.

TABLE OF CONTENTS

REVISION HISTORY **2**

TABLE OF CONTENTS **3**

ABBREVIATIONS **6**

1. INTRODUCTION **8**

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS **8**

2.1 Objectives 8
2.1.1 Primary Objective 8
2.1.2 Secondary Objective(s) 8
2.1.3 Exploratory Objective(s) 8
2.2 Estimands 8
2.3 Endpoints 10
2.3.1 Primary Endpoint(s) 10
2.3.2 Secondary Endpoint(s) 10
2.3.3 Exploratory Endpoint(s) 10

3. STUDY DESIGN **11**

3.1 General Description 11
3.1.1 Figure Study Flow Chart 13
3.2 Randomization 14
3.3 Blinding/Unblinding 14
3.4 Sample Size and Power Considerations 14

4. STATISTICAL ANALYSIS SETS **15**

4.1 Enrolled Set 15
4.2 Safety Analysis Set 15
4.3 Full Analysis Set 15
4.4 Per-Protocol Analysis Set 15
4.5 BAL Analysis Set 17
4.6 Per-Protocol BAL Analysis Set 18

5. STUDY SUBJECTS **18**

5.1 Disposition of Subjects 18

5.2 Demographic and Other Baseline Characteristics....19
5.3 Medical and Surgical History....19
5.4 Alpha1 Antitrypsin Deficiency History....20
5.5 Chest X-Ray and Computed Tomography....20
5.6 Prior Medications and Non-Drug Therapy....20
5.7 Prior Procedures....21
5.8 Concomitant Medications and Non-Drug Therapy....21
5.9 Concomitant Procedures....22
5.10 BAL Procedure....22
5.11 Exposure to Investigational Product....23
5.12 Measurements of Treatment Compliance....23
5.13 Protocol Deviations....24

6. EFFICACY ANALYSES....24

6.1 Analyses of Primary Efficacy Endpoints....25
6.1.1 Sensitivity Analyses of Primary Efficacy Endpoints....26
6.2 Multiplicity Adjustment....26
6.3 Analyses of Exploratory Endpoints....26

7. SAFETY ANALYSES....29

7.1 Adverse Events....29
7.1.1 COPD Exacerbation and Lower Respiratory Tract Infection....32
7.2 Immunogenicity....33
7.3 Clinical Laboratory Data....34
7.4 Vital Signs....37
7.5 Physical Examinations....37
7.6 12-lead Electrocardiogram....37

8. EXPOSURE ANALYSIS....38

8.1 Exposure Data....38
8.1.1 Exposure Endpoint and Analysis....38

9. OTHER ANALYSES....38

10. DATA MONITORING (REVIEW) COMMITTEE....38

11. DATA HANDLING CONVENTIONS....39

11.1 General Data Reporting Conventions....39

11.2 Definition of Baseline 39
11.3 Definition of Visit Windows 39
11.4 Derived Efficacy Endpoints 41
11.5 Repeated or Unscheduled Assessments of Safety Parameters 41
11.6 Handling of Missing, Unused, and Spurious Data 41
11.6.1 Missing Date of Investigational Product 41
11.6.2 Missing Date Information for Time Since First Diagnosis of Alpha1 Antitrypsin Deficiency History 42
11.6.2.1 Incomplete Date 42
11.6.3 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures) 42
11.6.3.1 Incomplete Start Date 42
11.6.3.2 Incomplete Stop Date 43
11.6.4 Missing Date Information for Adverse Events 44
11.6.4.1 Incomplete Start Date 45
11.6.4.2 Incomplete Stop Date 46
11.6.5 Missing Severity Assessment for Adverse Events 47
11.6.6 Missing Relationship to Investigational Product for Adverse Events 47
11.6.7 Character Values of Clinical Laboratory Variables 47
11.6.8 Handling of Randomization Errors 47

12. ANALYSIS SOFTWARE 48

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL 48

13.1 Planned Exploratory Analyses 48
13.1.1 Subgroup Analysis of the Primary and Exploratory [redacted] Endpoints ..48

14. REFERENCES 48

15. APPENDICES 49

15.1 Schedule of Activities 49
15.2 SAS Code 55

ABBREVIATIONS

Abbreviation	Definition
A1PI	$Alpha_1$-Proteinase Inhibitor
AE/AEs	Adverse Event/Adverse Events
AESI	Adverse Event Of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANEC	Anti-Neutrophil Elastase Capacity
ANOVA	Analysis Of Variance
AR/ARs	Adverse Reaction/Adverse Reactions
AST	Aspartate Aminotransferase
B19V	Parvovirus B19
BAL	Bronchoalveolar Lavage
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BW	Body Weight
C3	Complement Component 3
C4	Complement Component 4
CH50	50% Hemolytic Complement Activity of Serum
CI	Confidence Interval
CL	Confidence Limit
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ELF	Epithelial Lining Fluid
FAS	Full Analysis Set
FDA	Food And Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GGT	Gamma-Glutamyl-Transferase
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
Hct	Hematocrit
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IP	Investigational Product

IRT	Interactive Response Technology
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactic Dehydrogenase
LRTI	Lower Respiratory Tract Infection
MedDRA	Medical Dictionary For Regulatory Activities
NAT	Nucleic Acid Test
[redacted]	[redacted]
PCR	Polymerase Chain Reaction
PP	Per-Protocol
PT	Preferred Term (MedDRA)
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Standard Deviation
SI	System International
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

The purpose of the study is two-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 $Alpha_1$-Proteinase Inhibitor (A1PI) and [redacted] in the epithelial lining fluid (ELF) following IV administration at a dosage of 60 mg/kg body weight (BW)/week for 25 weeks in subjects with emphysema due to congenital A1PI deficiency.

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.

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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.

2.1.2 Secondary Objective(s)

- To collect additional safety information for GLASSIA.

2.1.3 Exploratory Objective(s)

- [redacted]

2.2 Estimands

The primary estimands are described in Table 1.

Table 1: List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	B: Variable (or endpoint)	C: Strategy for addressing intercurrent event	D: Population-level summary
Primary	The primary efficacy estimand is the effect of weekly IV augmentation therapy with GLASSIA on antigenic A1PI levels in ELF in subjects with congenital A1PI deficiency.	18 to 75 year-old subjects with A1PI-deficiency defined through study entry criteria and undergoing bronchoscopy/ bronchoalveolar lavage (BAL) procedures and following the requirements for the BAL analysis population as stated in the protocol	change from the baseline BAL visit to the on-treatment BAL visit in ELF antigenic A1PI levels, defined as the on-treatment BAL visit measurement minus the baseline BAL visit measurement	captured through the population definition (principal stratum strategy)	difference in mean change of ELF antigenic A1PI levels from the baseline BAL visit measurement to the on-treatment BAL visit measurement pooled across both treatment arms
Primary	The primary efficacy estimand is the effect of weekly IV augmentation therapy with GLASSIA on functional A1PI levels in ELF in subjects with congenital A1PI deficiency.	18 to 75 year-old subjects with A1PI-deficiency defined through study entry criteria and undergoing BAL procedures and following the requirements for the BAL analysis population as stated in the protocol	change from the baseline BAL visit to the on-treatment BAL visit in ELF functional A1PI levels, defined as the on-treatment BAL visit measurement minus the baseline BAL visit measurement	captured through the population definition (principal stratum strategy)	difference in mean change of ELF functional A1PI levels from the baseline BAL visit measurement to the on-treatment BAL visit measurement pooled across both treatment arms

2.3 Endpoints

2.3.1 Primary Endpoint(s)

Safety

1. Number (proportion) of adverse events (AEs) considered potentially related to the presence of 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. Change from baseline Antigenic A1PI levels in ELF.
2. Change from baseline Functional A1PI (also known as anti-neutrophil elastase capacity [ANEC]) levels in ELF.

2.3.2 Secondary Endpoint(s)

Safety

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

2.3.3 Exploratory Endpoint(s)

3. STUDY DESIGN

3.1 General Description

This is a Phase 3/4, prospective, 2-arm, double-blind, randomized, controlled, multicenter study to 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 FDA) for 25 weeks in approximately 36 A1PI-deficient subjects.

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 wash-out 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 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.

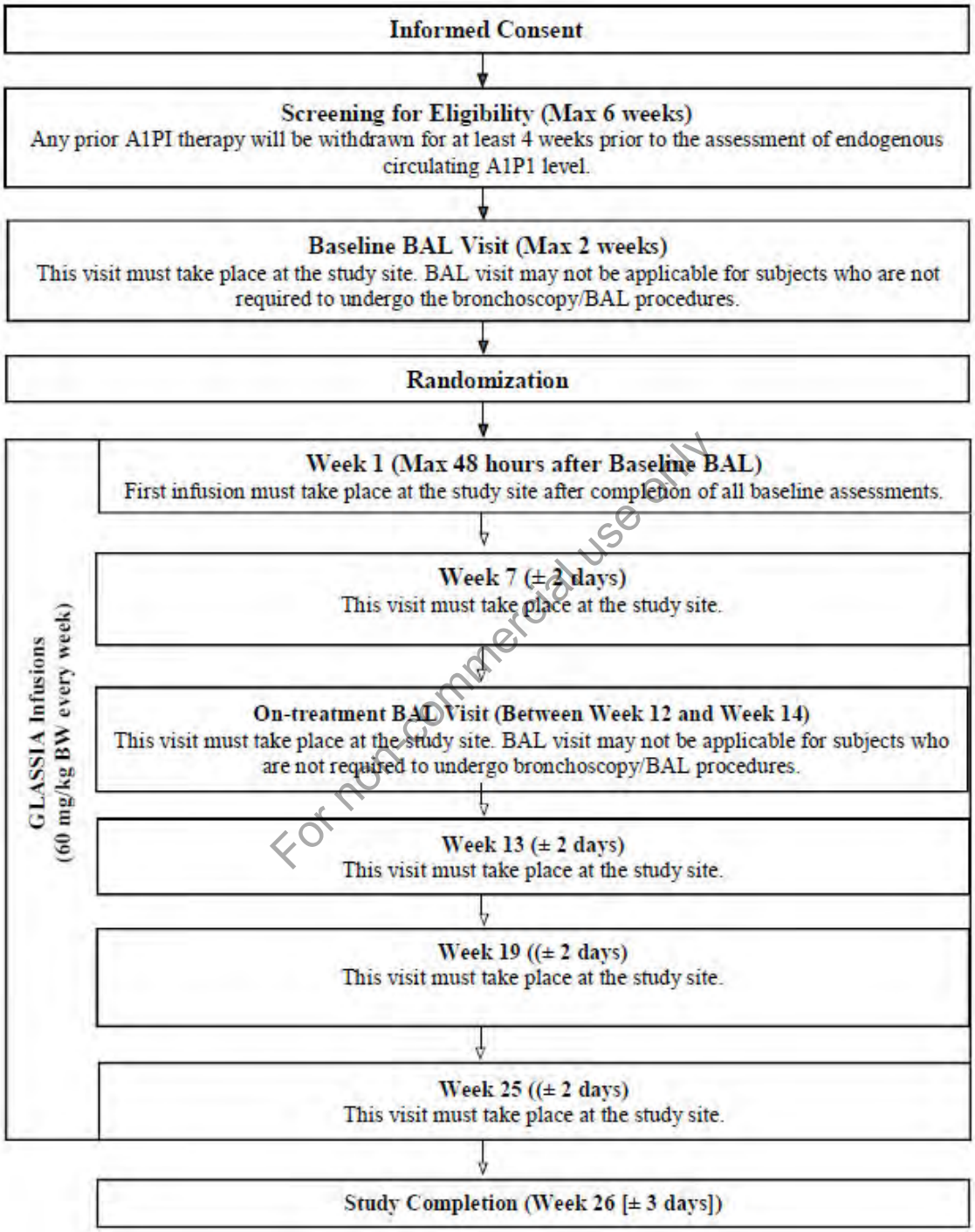
If for any reason the target of 15 to 18 evaluable subjects has not been achieved with the initial 36 randomized subjects, then additional subjects will be enrolled to meet the BAL enrollment target.

The duration of each subject's participation from enrollment to subject completion (i.e., last study visit) is anticipated to be approximately 8 months (unless the subject withdraws or is prematurely discontinued from the study). Subjects who have completed the baseline bronchoscopy/BAL visit and have acceptable BAL samples will be randomized in a 1:1 ratio to one of the 2 treatment arms: GLASSIA lot with particle loads representing the high end within the normal range or GLASSIA lot with particle loads representing the low end within the normal range. 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).

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 (i.e., 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 (e.g., 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 (i.e., 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. 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 follows the following flow chart:

3.1.1 Figure Study Flow Chart



3.2 Randomization

This is a 2-arm, double-blind, randomized, controlled clinical study. In order to minimize/avoid bias, subjects meeting all eligibility criteria will be randomly assigned to 1 of 2 treatment arms at a ratio of 1:1:

- Treatment Arm 1: GLASSIA lot with particle loads representing the high end within the normal range observed in GLASSIA lots manufactured
- Treatment Arm 2: GLASSIA lot with particle loads representing the low end within the normal range observed in GLASSIA lots manufactured

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 has been achieved and thus exempted from BAL procedures, randomization will take place upon confirmation of the main study eligibility criteria being met.

3.3 Blinding/Unblinding

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.

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 a serious adverse event (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 the treatment assignment of the specific individual subject involved in the emergency event via the centralized randomization service or from the unblinded biostatistician.

3.4 Sample Size and Power Considerations

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) 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 suffice 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 suffice 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 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.

4. STATISTICAL ANALYSIS SETS

4.1 Enrolled Set

The Enrolled Set will consist of all subjects who signed the informed consent.

4.2 Safety Analysis Set

The Safety Analysis Set will consist of all enrolled subjects who received any amount of investigational product (IP), regardless of protocol deviations or non-adherence to study procedures. Analysis will be performed according to the treatment regimen received, regardless of the randomized treatment regimen.

4.3 Full Analysis Set

The Full Analysis Set (FAS) will include all enrolled subjects who received at least 1 IP infusion and have at least 1 available antigenic or functional A1PI measurement (either from plasma or from ELF) during the treatment period. Analysis will be performed according to allocated treatment regimen regardless of the treatment regimen actually received.

4.4 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will include a subset of the Full Analysis Set, comprising subjects with no major/critical protocol deviations that may impact the efficacy assessments. For the purpose of statistical analysis, deviations that may impact efficacy will include, but will not be limited to, the following: did not meet all

inclusion/exclusion criteria, incorrect treatment applied (i.e. randomization error), 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, dose deviation of >10% for ≥4 consecutive infusions (missed infusions are counted), and use of an A1PI product (including commercially available GLASSIA) other than IP during the study treatment period. The PP Analysis Set will be discussed and approved at a data review meeting prior to unblinding and prior to database lock.

For the protocol deviation dataset, there are three levels of protocol deviation severity classifications with the following classifications:

Table 2: Severity Classifications of Protocol Deviations

Term	Definition
Critical Protocol Deviation	A deviation from Protocol-related procedures that threatens integrity of data, adversely affects subjects and/or could invalidate acceptability of a project (or part of it). Such deviations require immediate action.
Major Protocol Deviation	A deviation from Protocol-related procedures that could affect integrity of the data or adversely affect subjects. Such deviations require timely action.
Minor Protocol Deviation	A deviation from accepted procedures that will not adversely affect subjects or data integrity but should be dealt with appropriately.

The protocol deviation classification provided in Table 2 will have no impact on the assignment to the PP Analysis Set - only those deviations that may impact the efficacy assessments will be excluded from the PP Analysis Set. For the purpose of statistical analysis, subjects will be excluded from the PP Analysis Set based on occurrence of defined protocol deviations set out in Table 3 in accordance with the Protocol Deviation Management Plan. Additional major deviations not mentioned in Table 3 that may have an impact to efficacy assessments will be discussed in the data review meeting prior to unblinding and prior to database lock.

Table 3: Major/Critical Protocol Deviations That May Impact Efficacy Assessments

Category	Short Description	To be excluded from Per-Protocol Analysis
Eligibility and Entry Criteria	Subject randomized without meeting all inclusion criteria or meeting any exclusion criteria	Yes
Investigational Product Compliance	Subject misses a total of 2 or more consecutive weekly infusions and/or >15% of planned infusions	Yes
Investigational Product Compliance	Dose deviation of > ±10% of the calculated dose.	Yes
Study Procedure	Failure to comply with the washout period for pre-study A1PI augmentation therapy	Yes
Study Procedure	The subject took any A1PI augmentation therapy (other than the study IP) during the study	Yes

4.5 BAL Analysis Set

The BAL analysis set will include a subset of the FAS, 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 (i.e., 4 infusions within 35 days calculated from day of on-treatment BAL procedure as on-treatment BAL is scheduled one week after last infusion, 24h prior to the next scheduled IP infusion).
- Subjects must have available ELF data from acceptable BAL sample 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. An acceptable BAL sample is defined as at least 1 acceptable BAL sample obtained from any one of the 3 lobes from each visit and meeting the following criteria:
    - total recovery of ≥20% of the instilled volume of saline per lobe
    - BAL sample shows no blood by visual inspection

4.6 Per-Protocol BAL Analysis Set

The Per-Protocol BAL (PPBAL) Analysis Set is a subset of the BAL Analysis Set. Subjects who meet any of the following criteria, will be excluded from the PPBAL Analysis Set:

- Subjects who received an A1PI product (including commercially available GLASSIA) other than IP for the last 4 infusions prior to the on-treatment BAL procedure.
- Subjects with dose deviations >10% for the last 4 infusions prior to the on-treatment BAL procedure
- Subjects for whom the incorrect treatment (i.e. randomization error) was applied for the last 4 infusions prior to the on-treatment BAL procedure

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all Screen Failures (i.e., subjects that have signed the informed consent, but did not pass screening) will be presented.

A randomization assignment data listing will be provided for subjects that were randomized to a treatment group and actual treatment received based on the kit identification assignment will be included.

The number and percentage of subjects who were included in and excluded from each defined analysis set will be summarized by treatment group and pooled across both treatment arms; except for the Enrolled Set, which will be only summarized for overall number of subjects.

The number and percentage of subjects who completed and prematurely discontinued during the double-blind evaluation phase will be presented for each treatment group and pooled across both treatment arms for the Enrolled Set and BAL Analysis Set. Reasons for premature discontinuation from the double-blind evaluation phase as recorded on the termination page of the electronic case report form will be summarized (number and percentage) by treatment group and pooled across both treatment arms.

All subjects who prematurely discontinued during the double-blind evaluation phase will be listed by discontinuation reason for the Enrolled Set.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and characteristics at screening will be presented by treatment group and pooled across both treatment arms for the Safety Analysis Set, FAS, PP Analysis Set, BAL Analysis Set and PPBAL Analysis Set.

The following demographic characteristics will be summarized in the following order: age (years), age group (≤65, >65), sex, ethnicity, and race. The baseline characteristics will be summarized in the following order: weight (kg), height (cm), smoking history, forced vital capacity (FVC), FVC predicted, forced expiratory volume in 1 second (FEV1), FEV1 predicted, and FEV1/FVC. Age is calculated as the date of consent minus the date of birth, truncated to years. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group and pooled across both treatment arms for continuous variables. The number and proportion of subjects will be presented by treatment group and pooled across both treatment arms for categorical variables.

A listing of the demographic, baseline characteristics, and spirometry data will be provided using the Safety Analysis Set.

5.3 Medical and Surgical History

Medical and surgical history will be collected at Screening. Any preexisting diseases that are present before entry into the study and those that manifest with the same severity, frequency, or duration after IP exposure are described in the medical history. If an abnormal physical condition or 12-lead electrocardiogram is detected at screening, the condition will be described on the medical history. All medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or newer.

The number of subjects with any relevant past and current medical conditions/diseases will be tabulated by MedDRA system organ class (SOC) and preferred term (PT) by treatment arm and pooled across both treatment arms for the Safety Analysis Set. A subject will only be counted once within a particular SOC (or PT) even if he/she has multiple conditions/diseases in the same SOC (or PT). Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending frequency in the pooled treatment arms.

A listing of the data will be provided using the Safety Analysis Set.

5.4 Alpha1 Antitrypsin Deficiency History

Alpha1 antitrypsin deficiency history will be collected at the Screening. Subjects must have a diagnosis of A1PI deficiency (i.e., 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.

The alpha1 antitrypsin deficiency history will be summarized by the time since first diagnosis, number of pulmonary exacerbations in the past 52 weeks, complete or discontinued A1PI therapy for at least 4 weeks prior to screening, and frequency of different possible genotypes for the Safety Analysis Set.

A listing of the data will be provided using the Safety Analysis Set.

5.5 Chest X-Ray and Computed Tomography

A chest X-ray and computed tomography will be collected at the Screening. A listing of the data will be provided using the Safety Analysis Set.

5.6 Prior Medications and Non-Drug Therapy

Prior medications and non-drug therapies will be coded using World Health Organization (WHO) Drug Dictionary (Enhanced with WHO Herbal Dictionary) dated 01MAR2018 or newer.

Prior medication and non-drug therapy is defined as any medication or non-drug therapy with the start and stop date prior to the date of the first dose of investigational product.

The prior medication and therapies usage will be summarized by the number and proportion of subjects in each treatment group and pooled across both treatment arms within each ATC Term and Drug Preferred Name for the Safety Analysis Set. Subjects taking the same medication or therapy multiple times will only be counted once for that ATC Term or drug preferred name. Medications or therapies with start/stop dates that are partially/completely missing will be analyzed as described.

All prior medications and non-drug therapies will be listed for the Safety Analysis Set.

5.7 Prior Procedures

Prior procedures will be coded using MedDRA Version 21.0 or newer.

Prior procedure is defined as any procedure with the start and stop date prior to the date of the first dose of investigational product.

The prior procedures will be summarized by the number and proportion of subjects in each treatment group and pooled across both treatment arms by SOC and preferred term for the Safety Analysis Set. Multiple procedures by a subject in the same category will be counted only once. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending frequency in the pooled treatment arms.

All prior procedures will be listed for the Safety Analysis Set.

5.8 Concomitant Medications and Non-Drug Therapy

Concomitant medications and non-drug therapies will be coded using WHO Drug Dictionary (Enhanced with WHO Herbal Dictionary) dated 01MAR2018 or newer.

Concomitant medication or non-drug therapy is defined as any medication or non-drug with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusive.

Any medication or therapy with a start date that is over 72 hours after the date of the last dose of investigational product will be considered a post study treatment medication or non-drug therapy.

The concomitant medications and non-drug therapies will be summarized by the number and proportion of subjects in each treatment group and pooled across both treatment arms within each ATC Term and Drug Preferred Name for the Safety Analysis Set. Subjects taking the same medication or therapy multiple times will only be counted once for that ATC Term or drug preferred name. Medications or therapies with start/stop dates that are partially/completely missing will be analyzed as described.

All concomitant or post study treatment medications and non-drug therapies will be listed for the Safety Analysis Set.

5.9 Concomitant Procedures

Concomitant procedures will be coded using will be coded using MedDRA Version 21.0 or newer.

Concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of investigational product, inclusive. Any procedure with a start date that is over 72 hours after the date of the last dose of investigational product will be considered a post-treatment procedure.

The concomitant procedures will be summarized by the number and proportion of subjects in each treatment group and pooled across both treatment arms by SOC and PT for the Safety Analysis Set. Multiple procedures by a subject in the same category will be counted only once. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending frequency in the pooled treatment arms.

All concomitant or post-treatment procedures will be listed for the Safety Analysis Set.

5.10 BAL Procedure

A target of 15 to 18 evaluable 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. A subject must successfully complete the baseline BAL visit with verification of having evaluable samples collected [deficient plasma (antigenic) A1PI levels (≤11 μM)] before the randomization. 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. Subjects who have successfully completed the on-treatment BAL visit and have acceptable BAL samples (details in Section 11.4) 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.

All data from the BAL procedure will be listed for the BAL Analysis Set. The subjects that were considered as BAL evaluable subjects will be flagged in the data listing.

5.11 Exposure to Investigational Product

Exposure to investigational product for the Safety Analysis Set will be summarized in terms of treatment duration (days), which is calculated as the number of days from the date of first dose of investigational product taken to the date of the last dose of investigational product taken, inclusively. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the exposure to investigational product by treatment group and pooled across both treatment arms.

A listing will be created by subject number and visit giving the date and time of dose administration and other infusion-related information as collected based on the Safety Analysis Set.

5.12 Measurements of Treatment Compliance

Treatment compliance will be summarized for the Safety Analysis Set.

Compliance regarding number of infusions
The compliance measures regarding number of infusions are defined as:

1) The total number of applied infusions for each subject during the study divided by 25 (i.e. the number of expected infusions during the study) multiplied by 100.

2) The total number of applied infusions for each subject during the study divided by the number of expected infusions multiplied by 100 (in case a subject discontinued from the study, only the time the subject was in the study will be taken into account).

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the compliances regarding number of infusions by treatment group and pooled across both treatment arms.

Compliance regarding change of infusion rate / interruption of infusion:
The number and proportion of subjects with at least one infusion rate change or one infusion rate interruption will be summarized by treatment and pooled across both treatment arms.

Compliance regarding dose:
The compliance measure regarding dose is calculated as the number of infusions within 10% of the planned dose of 60 mg/kg divided by the total number of applied infusions.

For the calculation of the body weight adjusted dose the latest available body weight (kg) before the infusion will be used.

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the compliance regarding the dose by treatment group and pooled across both treatment arms.

A listing of treatment compliance will be provided for all subjects in the Safety Analysis Set.

5.13 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database. IQVIA/Takeda will classify protocol deviations per the agreed protocol deviation management plan. The Takeda study team will review the protocol deviations and their classification throughout the study and before treatment unblinding and database lock. Decisions of the review will include the accuracy of protocol deviations categorization based on the clinical and medical team review of the clinical database. Confirmed categorization of protocol deviations will be documented in the Protocol Deviation tracker for the study.

Protocol deviations will be summarized by category, severity and site for each treatment group and pooled across both treatment arms for the Enrolled Set.

Protocol deviations will be listed for the Enrolled Set. In addition, a separate protocol deviation listing will be provided for deviations that are related to COVID-19.

6. EFFICACY ANALYSES

All efficacy analyses described in this section that are related to ELF will be based on the BAL Analysis Set according to the pooled treatment across both assigned treatment arms. In addition, sensitivity analyses based on the PPBAL Analysis Set will be performed for all efficacy analyses that are related to ELF. The sensitivity analyses will only be performed if the BAL Analysis Set differs from the PPBAL Analysis Set. For the sensitivity analyses, the same tables will be created as defined in Section 6.1.

All efficacy analyses described in this section that are related to plasma will be based on the Safety Analysis Set according to the actual treatment received separately by each treatment arm as well as pooled across both treatment arms. In addition, all efficacy analyses that are related to plasma will be repeated based on the PP Analysis Set. These

repeated analyses will only be performed in case the Safety Analysis Set differs from the PP Analysis Set.

Baseline (Baseline BAL) for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product (start date and time of the first infusion).

6.1 Analyses of Primary Efficacy Endpoints

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. This approach is based on the fact that urea is freely diffusible through most body compartments, including the alveolar wall. A dilution factor related to urea will need to be applied to the results prior to the analysis. The 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 will be corrected accordingly.

The antigenic and functional A1PI levels in the ELF will be collected during the baseline BAL visit and the on-treatment BAL visit.

Since an increase from baseline in the mean ELF levels of antigenic/functional A1PI is expected, an upper 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/functional A1PI from baseline BAL to the on-treatment BAL measurement is μ_d:

H_0: Mean change in antigenic/functional 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/functional A1PI in the ELF from baseline to the on-treatment measurement will be greater than zero.

$$H_1: \mu_d > 0$$

where μd = on-treatment antigenic (or functional) A1PI in the ELF - baseline antigenic (or functional) A1PI in the ELF.

A mixed-effect model with visit as fixed effect and subject as a random effect will be used for the 1-sided paired t-test. The least squared mean difference between on-

treatment BAL to baseline BAL and corresponding p-value will be provided. In addition, the 2.5% lower limit of the one-sided confidence interval for the difference will be reported. The SAS code of the mixed-effect model can be found in Section 15.2.

The natural logarithm transformation may be applied to the ELF antigenic or functional A1PI values prior to analysis if the distributions are highly skewed.

No missing data imputation will be performed.

ELF antigenic and functional A1PI levels, as well as changes from baseline, will be summarized descriptively and displayed graphically based on data pooled across both treatment arms.

Changes from baseline in ELF antigenic and functional A1PI levels will also be summarized for the following subgroups: by site, sex, age group (≤65; >65), race, and ethnicity. [redacted]

Listings of all antigenic and functional A1PI levels in the ELF will be provided for the BAL Analysis Set. Unacceptable measurements (and therefore not used for the analysis) will be flagged and the reason for non-acceptance will be provided.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoints

A sensitivity analysis will be done on the PPBAL Analysis Set for the primary efficacy endpoints. This analysis will only be performed if the BAL Analysis Set differs from the PPBAL Analysis Set. For the sensitivity analyses, the same tables will be created as defined in Section 6.1.

6.2 Multiplicity Adjustment

No multiplicity adjustment will be applied in the efficacy analysis.

6.3 Analyses of Exploratory Endpoints

[redacted]

[redacted]

o.

[redacted]

[redacted]

[redacted]

7. SAFETY ANALYSES

All safety analyses will be based on the Safety Analysis Set according to the treatment the subject actually received separately by each treatment arm as well as pooled across both treatment arms. For each safety variable, the last value collected before the first dose of investigational product (start date and time of the first infusion) will be used as baseline.

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 21.0 or newer.

Any AE that occurs on or after the first dose of IP infusion will be considered a treatment-emergent adverse event (TEAE).

An overall summary of the number of subjects with any TEAE as well as the number of events will be presented. The table will include:

- TEAEs
- Serious TEAE
- TEAEs leading to death
- Maximum severity of TEAEs
- TEAEs related to IP
- TEAEs that are considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution
- TEAEs related to study procedure
- TEAEs leading to discontinuation
- Temporally associated TEAEs within 24 hours [i.e. TEAEs that begin(a) during or within 24 hours (or 1 day where time of onset is not available) following the end of the IP infusion irrespective of being related or not related to treatment]
- Temporally associated TEAEs within 72 hours [i.e. TEAEs that begin(a) during or within 72 hours (or 3 days where time of onset is not available) following the end of the IP infusion irrespective of being related or not related to treatment]
- Treatment-emergent ARs plus suspected ARs within 24 hours
- Treatment-emergent ARs plus suspected ARs within 72 hours

- Immune-mediated TEAEs

Definition of TEAEs that are considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution:

A TEAE that is considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution is defined as any embolic or thrombotic event.

Definition of treatment-emergent ARs plus suspected ARs:
A treatment-emergent AR plus suspected AR is any TEAE which meet any of the following criteria:

(a) an AE that began during infusion or within 72 hours (or 3 days where time of onset is not available) 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 treatment-emergent ARs plus suspected ARs which met any of the following criteria:

(a) an AE that began during infusion or within 24 hours (or 1 day where time of onset is not available) 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.

Definition of immune-mediated TEAEs:

An immune-mediated TEAE is a TEAE which may have resulted from an immune-mediated response, categorized under hypersensitivity based on list of preferred term (PT) provided by the Takeda medical.

The overall TEAEs summary will also be provided by sex, age group (≤65; >65), race, and ethnicity.

Additionally, 95% two-sided Clopper-Pearson exact confidence intervals will be calculated for the following quantities, using the SAS code for calculation of confidence intervals which is presented in Section 15.2:

- the number of subjects with serious TEAEs
- the number of subjects with related TEAEs
- the number of subjects with TEAEs that are considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution
- the number of subjects with temporally associated TEAEs within 24 hours
- the number of subjects with temporally associated TEAEs within 72 hours
- the number of subjects with treatment-emergent ARs plus suspected ARs within 24 hours
- the number of subjects with treatment-emergent ARs plus suspected ARs within 72 hours
- the number of subjects with immune-mediated TEAEs

In addition, tables of TEAEs will be prepared to list each PT, the number of subjects who experienced a PT at least once, the rate of subjects with PT(s). The PTs will be grouped by system organ class. For the severity and related table, each event will then be divided into defined severity grades (mild, moderate, severe). When a single subject experiences multiple AEs categorized under the same preferred term and causality assessment, this AE is shown only once at its most serious severity. The table will also divide the AEs into those considered related (a "possibly related" or a "probably related" AE will be considered as a "related AE") to the treatment and those considered unrelated (an "unlikely related" or a "not related" AE will be considered as an "unrelated" AE). The severity and related table will also include the Subject IDs with the respective PT. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending frequency in the pooled treatment arms. Similar tabulation of data will be conducted for:

- Serious TEAEs
- Temporally associated TEAEs within 24 hours
- Temporally associated TEAEs within 72 hours
- Treatment-emergent ARs plus suspected ARs within 24 hours
- Treatment-emergent ARs plus suspected ARs within 72 hours
- TEAEs that are considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution
- Immune-mediated TEAEs

The number and proportion of infusions (defined as percentage of the total number of infusions administered) temporally associated (within 24 hours/ within 72 hours) with TEAEs/serious TEAEs will be computed for each subject. The median (95% CI), minimum, and maximum will be presented.

The number and proportion of infusions (defined as percentage of the total number of infusions administered) causally associated with TEAEs/serious TEAEs will be computed for each subject. The median (95% CI), minimum, and maximum will be presented.

The number and proportion of infusions (defined as percentage of the total number of infusions administered) associated with related TEAEs will be computed for each subject. The median (95% CI), minimum, and maximum will be presented.

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

Listings of all TEAEs will be provided for the Safety Analysis Set. In addition, separate listings will be created based on the Safety Analysis Set for:

- all serious TEAEs
- all treatment emergent ARs plus suspected ARs
- all TEAEs that are considered potentially related to the presence of protein aggregates (particle load) in the GLASSIA solution
- all immune-mediated TEAEs

Pre-treatment events (captured on the AE form that occurred prior to the first dose of investigational product) will be listed by subject for all subjects who were treated with IP (i.e. Safety Analysis Set). In addition, adverse events of subjects who were never treated with IP will be listed.

Imputed dates, severity and relationship to investigational product (see Section 11.6.3, Section 11.6.4 and Section 11.6.5 respectively for imputation rules) will be marked in the listings.

7.1.1 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 lower respiratory tract infection (LRTI) symptoms are no longer clinically evident (i.e., the first day that a subject returns to his/her usual clinical state) for at least 2 consecutive days. 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.

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 (e.g., 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.

The number and percentage of subjects reporting COPD exacerbation and/or lower respiratory tract infection will be summarized by most extreme severity, number of exacerbations, average duration, and number of hospitalizations.

Listings of all pulmonary exacerbations will be provided.

7.2 Immunogenicity

The number and proportion of subjects who develop binding and/or neutralizing anti-A1PI antibodies will be summarized with their point estimates and 95% two-sided Clopper-Pearson exact confidence intervals. The SAS code for calculation of the confidence interval can be found in Section 15.2.

Immunogenicity will also be summarized by sex, age group (≤65; >65), race, and ethnicity.

All immunogenicity data will be listed for the Safety Analysis Set. All antibody results from subjects who had any positive binding or neutralizing anti-A1PI data at any time point will be listed along with the corresponding plasma antigenic and functional A1PI levels in the individual subject. Additionally, to assess the temporal relationship of anti-A1PI antibody formation with potentially immune-mediated TEAEs, the data listing will

flag any subjects who had any immune-mediated TEAE and correspond the reviewer to the immune-mediated TEAEs data listing for further details related to corresponding immune-mediated TEAEs.

7.3 Clinical Laboratory Data

The clinical laboratory assessments will include the following:

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

Chemistry
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.

Urinalysis
Color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination (RBC, WBC, bacteria, casts).

Complement Activation and Immune Complex
Serum complement component 3 (C3), complement component 4 (C4), total complement (50% hemolytic complement activity of serum; CH50), and C1q binding assay for circulating immune complexes.

Viral Serology and Nucleic Acid Tests
HAV, HBV, HCV and HIV1/HIV2 by serology for antigenemia or antibodies or by polymerase chain reaction (PCR) based NAT, towards eligibility determination. Viral testing for B19V will consist of B19V antibody serology test and NAT, based on real-time PCR detection of B19V DNA.

The clinical laboratory data will be summarized for each visit by descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for continuous variables and the number and proportion of subjects in each category for categorical variables.

The clinical significance of abnormal laboratory values as assessed by the investigator is captured in the source documents:

- The clinical significance of abnormal laboratory values that occurred prior to the first infusion will be reported as medical history if considered as clinically significant by the investigator.
- The clinical significance of abnormal laboratory values that occurred during or after the first infusion will be reported as an AE if considered as clinically significant by the investigator.

In addition to the investigator assessment, criteria for clinical significance (CS) were defined for some of the clinical laboratory tests (see Table 4).

Shift tables from baseline of normal versus abnormal low/high laboratory values to each visit will be presented. In addition, shift tables (of laboratory assessments provided in Table 4) from baseline of normal versus abnormal clinically significant/not-clinically significant laboratory values to each visit will be presented. Results of laboratory tests defined in Table 4 that are out of range and do not meet the thresholds according to Table 4 will be classified as not-clinically significant.

Table 4: Criteria for Abnormal Clinically Significant Laboratory Tests

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	

Laboratory Test	Lowest Alert Limit	Highest Alert Limit	Comment
LDH	---	>3x ULN	
GGT	---	>3x ULN	
Bilirubin (total and indirect)	---	>3x ULN	
Serum creatinine	---	(M) >2.0 mg/dL (F) >1.6 mg/dL	
CPK	---	>5x ULN	
Glucose	<30 mg/dL	>200 mg/dL	Hyperglycemia should be interpreted in the context of known diabetes as a comorbidity
Serum albumin	<3.0 g/dL	----	May indicate protein loss, inflammation or malnutrition
Complement Activation and Immune Complex			
Serum C3	<70 mg/dL	---	
Serum C4	<14 mg/dL	---	
Total complement (CH50)	<30 U/ml	---	
C1q binding/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.

The number and proportion of subjects with confirmed treatment-emergent seroconversion (negative or missing at Baseline and confirmed positive at any post-infusion time point) by viral serology or nucleic acid test for B19V (Parvovirus B19 IgG Antibody, Parvovirus B19 IgM Antibody, Parvovirus B19 DNA Quant RT-PCR) during or following treatment with GLASSIA will be summarized with point estimates, percentages, and 95% two-sided Clopper-Pearson exact confidence intervals. Indeterminate results will be set to missing. The SAS code for calculation of the confidence interval can be found in Section 15.2.

All laboratory data will be listed for the Safety Analysis Set. In addition, a listing of subjects with post-baseline CS values will be provided including the subject number, site, baseline, and all corresponding post-baseline values for the specific laboratory test.

All laboratory tables will include results from central laboratory only. Results from the local laboratories (if any) will be only listed.

7.4 Vital Signs

Descriptive statistics of vital signs (systolic and diastolic blood pressure, body temperature, respiratory rate, pulse rate, and weight) will be performed. The changes in vital signs obtained pre- and post-infusions and pre- and post-BAL procedures will be also summarized.

All vital sign data will be listed for the Safety Analysis Set. A separate data listing will include vital sign measurements that were flagged for 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)

7.5 Physical Examinations

A physical examination will be performed at screening and at planned assessment study visits 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 page. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF page.

7.6 12-lead Electrocardiogram

A 12-lead electrocardiogram will be performed at screening and at planned assessment study visits, if needed. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF page. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF page.

8. EXPOSURE ANALYSIS

8.1 Exposure Data

8.1.1 Exposure Endpoint and Analysis

Plasma trough antigenic and functional A1PI levels, as well as changes from baseline, will be summarized descriptively by visit including study completion visit (Week 26) and Early Termination Visit as separate visits, and displayed graphically based on data separately by treatment arm as well as pooled across both treatment arms for the FAS and PP Analysis Set. Plasma antigenic and functional A1PI levels obtained at the baseline and on-treatment BAL visits will be summarized separately pooled across both treatment arms for the BAL and PPBAL Analysis Set.

The plasma concentration samples will also be correlated with the corresponding values in the ELF at baseline and on-treatment BAL visits by calculating the Pearson correlation coefficient and displayed graphically. These analyses will be conducted with both the BAL and the PPBAL Analysis Set. The SAS code for calculation of the correlation coefficient can be found in Section 15.2.

Changes from baseline in plasma antigenic and functional A1PI levels will also be summarized for the following subgroups: by sex, age group (≤65; >65), race, and ethnicity for the FAS and the PP Analysis Set.

In the event that anti-A1PI antibody formation is detected, the individual antigenic and functional A1PI levels will be evaluated in conjunction with binding and neutralizing anti-A1PI antibody titers, in a separate data listing.

All exposure data will be listed for the Safety Analysis Set.

9. OTHER ANALYSES

No other analyses are planned for this study.

10. DATA MONITORING (REVIEW) 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. The DMC will not review efficacy data. 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.

No formal interim analysis for efficacy will be performed.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation (SD), minimum, and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Means and medians will be displayed with one decimal place beyond the collected data, and SDs will have 2 decimal places beyond the collected data. Minimums and maximums will be displayed with the same number of decimal places as the collected data. For discrete variables, population size (N for analysis set size and n for available data) and percentage will be presented. Percentages will be displayed with 1 decimal place. The p-values will be displayed as 3 decimal places and will round 0.000 as <0.001.

The change from baseline will be calculated as the post baseline assessment minus the baseline assessment.

11.2 Definition of Baseline

Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product (based on dates or date/times).

11.3 Definition of Visit Windows

Assessments of specific visits will be used in the statistical tables only if they fall within the visit windows as described in Table 5 below (see “Start Day of Window for Statistical

Analysis" and "End Day of Window for Statistical Analysis"); the visit windows that will be used for the statistical analyses have been designed to maximize the number of subjects and amount of data to be included, without any impact on the outcomes of the study. In case a visit does not fall into the corresponding visit window for statistical analysis, corresponding results will be only listed and flagged.

Study day will be calculated as follows:

- If the assessment date is on or after the date of first dose of IP:

  Study day = assessment date – first dosing date + 1

- If the assessment date is before the date of first dose of IP:

  Study day = assessment date – first dosing date

Table 5: Analysis Visit Windows (Study Day Based)

Visit	Planned Study Day	Start Day of Window per Protocol	End Day of Window per Protocol	Start Day of Window for Statistical Analysis	End Day of Window for Statistical Analysis
Screening	-1	Informed Consent	Before first IP infusion	Informed Consent	Before first IP infusion
Week 1 (i.e. Baseline)	1	1	1	1	1
Week 7	43	41	45	39	47
Week 13	85	83	87	81	89
Week 19	127	125	129	123	131
Week 25	169	167	171	165	173
Week 26	176	173	179	169	183
BAL Visits					
Baseline BAL	within 48hours prior to first IP infusion	-2	1 (prior to first IP infusion)	-	1 (prior to first IP infusion)
On-Treatment BAL (Week 12-Week 14)	78 to 92	76	94	-	-

Example of calculated planned study day / Week 13: (12*7)+1=85

11.4 Derived Efficacy Endpoints

Antigenic and functional A1PI levels in the ELF, [redacted] are collected at baseline BAL and on-treatment BAL. An acceptable BAL sample is defined as at least 1 acceptable BAL sample obtained from any one of the 3 lobes from each visit and meeting the following criteria:

- total recovery of ≥20% of the instilled volume of saline per lobe
- BAL sample shows no blood by visual inspection

For acceptable BAL sample, 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). The values will be reported in units of molarity (micromolar). [redacted] The molecular weight of A1PI is 52,000 Daltons, [redacted] The molarity is calculated as (concentration in g/L) / (molecular weight in Daltons). The average values of each acceptable measurement within each subject and BAL visit will be used for the analysis of the efficacy endpoints.

11.5 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. Additional post-baseline repeated, or unscheduled assessments will not be included in the by-visit summary tables, but will be included in subject listings. Assessments that were not mapped to any analysis window (including repeated or unscheduled assessments) will not be included in the analyses. However, all post-baseline assessments will be used for CS value determination and all assessments will be presented in the data listings.

11.6 Handling of Missing, Unused, and Spurious Data

No missing data imputation will be performed for the efficacy observations.

11.6.1 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Analysis Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

11.6.2 Missing Date Information for Time Since First Diagnosis of Alpha1 Antitrypsin Deficiency History

For alpha1 antitrypsin deficiency history, incomplete (i.e., partially missing) date for time since first diagnosis will be imputed.

11.6.2.1 Incomplete Date

The following rules will be applied to impute the missing numerical fields.

11.6.2.1.1 Missing Day and Month

- If year of the incomplete date is confirmed to be before the year of the informed consent, then December 31 will be assigned to the missing fields.

11.6.2.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.2.1.3 Missing Day Only

- If the year of the incomplete date is before the year of the informed consent, or if both years are the same but the month is before the month of the date of the informed consent, then the last day of the month will be assigned to the missing day.

11.6.3 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications, non-drug therapies, and procedures, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

11.6.3.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

11.6.3.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

11.6.3.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.3.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of investigational product, or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of investigational product, or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

11.6.3.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

11.6.3.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

11.6.3.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.3.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of investigational product, or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the last dose of investigational product, or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

11.6.4 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to impute only incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

11.6.4.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

11.6.4.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

11.6.4.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.4.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of investigational product, or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of investigational product, or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

11.6.4.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

11.6.4.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

11.6.4.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.4.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of investigational product, or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the last dose of investigational product, or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

11.6.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be used in data listings.

11.6.6 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

11.6.7 Character Values of Clinical Laboratory Variables

For the antigenic and functional AIPI results in plasma and ELF, values of below the lower limit of quantification (LLOQ) will be set to half of the LLOQ. For all other laboratory data, values of below the lower limit of quantification (LLOQ) will be set to LLOQ. However, the actual values as reported in the database will be presented in data listings.

11.6.8 Handling of Randomization Errors

If a subject is randomized inadvertently due to user misunderstanding of the IRT system, did not met the study entry criteria, discontinued the same day they were randomized, and never received treatment, the subject will be considered a screen failure and will not be included in any analyses except those involving the Enrolled Set. However, because they were randomized in the IRT system they will be included in the randomization assignment data listing, including treatment arm assignment, but flagged/identified as randomization errors.

12. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

13.1 Planned Exploratory Analyses

[redacted]

13.1.1 Subgroup Analysis of the Primary and Exploratory [redacted] Endpoints

The change from baseline in ELF and plasma antigenic and functional A1PI levels, as well as [redacted], will be also summarized by site for the subgroup summaries.

14. REFERENCES

Data Monitoring Committee Charter; Protocol: 471101; Version 1.0, 04Dec2018.

15. APPENDICES

15.1 Schedule of Activities

Table 6: Schedule of Study Procedures and Assessments

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]	
Anti-A1PI Antibodies[m,n]			X[g]			X[g]		X[g]	X
Weekly GLASSIA Infusions[o]			X →						

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]**
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 Protocol; 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 Protocol; 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 Protocol; Section 10.4 for more details).

[c] Subjects who are being discontinued from the study early and having been exposed to IP will be asked to return to the study site 7±3 days after the last infusion for early termination assessments. Subjects who are discontinued early from the study prior to receiving any IP administration will not need to undergo early termination procedures, except for those subjects who have undergone the baseline BAL procedure in which case subjects will be followed for potential post-BAL complications for a period of time in accordance with local institutional standard practice but not to exceed 30 days.

[d] Written informed consent must be obtained prior to performance of any study procedures including screening/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 (i.e., 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 (e.g., >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.

Continued on Next Page

Continued

[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 (e.g., 400 µg of salbutamol, or its equivalent).

[l] For laboratory assessments, see table below.

[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 (e.g., 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.

Table 7: Schedule of Clinical Laboratory Assessments

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
[redacted]			P[e]	P[e]		P[e]	P[e]	P[e]	

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]**
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].

Continued on Next Page

Continued

[a] For subjects undergoing bronchoscopy/BAL procedures (see Protocol; 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 Protocol; Section 10.4 for more details).

[b] The on-treatment BAL procedure will be performed between Week 12 and Week 14 (see Protocol; 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 Protocol; 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 (i.e., red blood cell [RBC]) count, leukocytes (i.e., white blood cell [WBC]) count with differential (i.e., 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 (e.g., Week 25) is required. Any evidence of seroconversion (e.g., 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.

15.2 SAS Code

1. The following SAS® code will be used for the mixed-effect model of the primary efficacy endpoints, antigenic/functional A1PI levels in ELF, [redacted]

```
proc mixed data=<ds>;
  class visit subjid;
  model <result>=visit;
  random subjid;
  /* p-value for the upper test: */
  estimate "Week 12 - Baseline BAL" visit -1 1 / cl e alpha=0.025 upper;
  LSmeans visit;
run;
```

where:
<ds> refers to the input dataset
<result> refers to the actual result for antigenic A1PI levels in ELF, functional A1PI levels in ELF [redacted]

[redacted]

2. The following SAS® code will be used for 95% two-sided Clopper-Pearson exact confidence intervals:

```
proc freq data=<ds>;
by treatment <category>;
tables <result>/ binomial (exact level='Yes') alpha=0.05;
exact binomial;
run;
```

where:
<ds> refers to the input dataset
<category> refers to the specific category as defined for the AEs, immunogenicity, viral serology, or nucleic acid test for B19V
<result> refers to “No” or “Yes” for each category

3. The following SAS® code will be used for Pearson correlation coefficient:

```
proc corr data=<ds>;
by timepoint;
var <plasma> <ELF>;
run;
```

where:
<ds> refers to the input dataset
<plasma> refers to the actual result or change from baseline result for plasma antigenic A1PI levels or plasma functional A1PI levels
<ELF> refers to the actual result or change from baseline result for antigenic A1PI levels in ELF or functional A1PI levels in ELF