Official Title:	A Multi-center, Single-Dose and Repeat-Dose Over Eight Weeks, Sequential Cohort Study to Evaluate Safety and Tolerability as well as Pharmacokinetics of Two Different Doses of Alpha1-Proteinase Inhibitor Subcutaneous (Human) 15% Administered Subcutaneously in Subjects with Alpha1-Antitrypsin Deficiency
NCT Number:	NCT04722887
Document Date:	Protocol, Version 7.0: 19-Sep-2024

Completion of the signature block below signifies the review and approval of this document.

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[redacted]	Owner	19-Sep-2024 13:36:33

Clinical Study Protocol

Protocol Title:	A Multi-center, Single-Dose and Repeat-Dose Over Eight Weeks, Sequential Cohort Study to Evaluate Safety and Tolerability as well as Pharmacokinetics of Two Different Doses of Alpha$_1$-Proteinase Inhibitor Subcutaneous (Human) 15% Administered Subcutaneously in Subjects with Alpha$_1$-Antitrypsin Deficiency
Test Product:	Alpha$_1$-Proteinase Inhibitor Subcutaneous (Human), 15% (Alpha-1 15%)
Sponsor's Name and Address:	Grifols Therapeutics LLC 79 TW Alexander Drive Research Triangle Park, NC 27709
Additional Identifier:	Alpha-1 15% Safety and PK Study
Protocol Number:	GC2008
IND Number:	19613
Development Phase:	1/2
Sponsor Signatories:	[redacted] See Sponsor Signatures on the cover page of the protocol

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PROTOCOL VERSION HISTORY

Protocol Version	Date of Approval/Effective Date
7.0 Amendment 6 + Integrated Protocol	See left margin
6.0 Amendment 5 + Integrated Protocol	25 Oct 2023
5.0 Amendment 4 + Integrated Protocol	09 Aug 2023
4.0 Amendment 3 + Integrated Protocol	23 Dec 2022
3.0 Amendment 2 + Integrated Protocol	21 Jun 2022
2.0 Amendment 1 + Integrated Protocol	24 Jan 2022
1.0 Original	29 Jul 2020

Amendment 6

The protocol for GC2008 (Amendment 5, Version 6.0, dated 25 Oct 2023) has been amended as Protocol Amendment 6, Version 7.0. See Appendix 3 for a summary of changes for Protocol Amendment 6.

PROTOCOL SYNOPSIS

Title of Study:

A Multi-center, Single-Dose and Repeat-Dose Over Eight Weeks, Sequential Cohort Study to Evaluate Safety and Tolerability as well as Pharmacokinetics of Two Different Doses of Alpha$_1$-Proteinase Inhibitor Subcutaneous (Human) 15% Administered Subcutaneously in Subjects with Alpha$_1$-Antitrypsin Deficiency

Study Number:

GC2008

Phase:

1/2

Study Objectives:

Primary Objective

To evaluate the safety and tolerability of 72 mg/kg and 180 mg/kg Alpha-1 15%, administered as a single-dose subcutaneous (SC) infusion and subsequently as weekly SC infusions over 8 weeks in subjects with Alpha$_1$-Antitrypsin Deficiency (AATD).

Pharmacokinetic Objective

The pharmacokinetic (PK) objective is to evaluate the PK of Alpha$_1$-proteinase inhibitor (Alpha$_1$-PI), measured using both antigenic content and functional activity assays, following a single-dose SC infusion and subsequently eight weekly SC infusions of 72 mg/kg or 180 mg/kg Alpha-1 15% in subjects with AATD.

Exploratory Objective

The exploratory objective of this study is to assess subject satisfaction with SC treatment following 8 weeks of SC doses of 72 mg/kg or 180 mg/kg Alpha-1 15% in subjects with AATD.

An additional exploratory PK objective is to evaluate the PK of Alpha$_1$-PI, measured using both antigenic content and functional activity assays, following 8 weekly intravenous (IV) infusions of 60 mg/kg or 120 mg/kg Liquid Alpha$_1$-PI in subjects with AATD.

Overall Study Design and Description:

This is a multi-center, single-dose followed by a repeat-dose over 8 weeks, sequential cohort study evaluating safety and tolerability as well as PK of 2 different doses of Alpha$_1$-PI SC (human) 15% administered SC as Alpha$_1$-PI augmentation in subjects with AATD.

An internal safety review committee (iSRC), comprised of impartial and independent members at least the Grifols medical monitor or qualified medical designee, pharmacovigilance, and a third individual of the study team such as someone knowledgeable in the epidemiological field or, knowledgeable in the therapeutic area, or a statistician will be established to monitor the progress and the safety of the clinical trial participants, as well as any pump related issues. The iSRC charter will outline the composition, responsibilities, schedule of the iSRC meetings, and study stopping rules. At a minimum, the iSRC will convene to review subject data, including but not limited to

demographics, dosing, concomitant medications, hematology and chemistry, and adverse events (AEs) to confer and document agreement that the next dose level is considered appropriate and safe.

Approximately 16 Alpha$_1$-PI augmentation subjects aged 18 years and older will be enrolled. Enrollment will occur in 2 sequential dose cohorts of approximately 8 subjects each.

Subjects cannot enroll into both cohorts.

The first cohort will include approximately 8 subjects receiving the 72 mg/kg (Cohort 1) starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose), safety data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (60 mg/kg for Cohort 1) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 1. Following completion of Treatment Period 2 (Repeat-Dose) for subjects in Cohort 1, the iSRC will evaluate safety data prior to initiating Cohort 2 (180 mg/kg). Dosing must not commence to Cohort 2 until Grifols has provided written confirmation to the principal investigators (PI). If the iSRC determines it is safe to proceed with dose escalation, Cohort 2 will be initiated.

The second cohort will include approximately 8 subjects receiving the 180 mg/kg (Cohort 2) dose of Alpha-1 15% starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). Furthermore, enrollment into Cohort 2 will only commence once the iSRC has reviewed safety data from the entire cohort of subjects treated with 72 mg/kg. To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose) phase, safety data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (120 mg/kg for Cohort 2) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) from a subset of subjects will be evaluated by the study team to determine/confirm the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 2.

Furthermore, within each cohort dosing will be staggered subject by subject for the first 4 subjects with a 7-day waiting period in between each subject, to allow assessment of the

safety and tolerability by the iSRC. If the iSRC determines it is appropriate and safe, the last 4 subjects within the cohort can be enrolled without the staggered approach.

Dose-limiting toxicities (DLTs) will be assessed by the investigator based on toxicity grade according to the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5.0), clinical significance, and possible relationship to study drug. The DLT evaluation period for the determination of the next dose level will be in the first 7 days immediately following the first SC injection.

Number of Subjects Planned:

Approximately 16 Alpha$_1$-PI augmentation subjects (2 cohorts with approximately 8 unique subjects per cohort) aged 18 years and older will be enrolled.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

A subject must meet all the following inclusion criteria to be eligible for participation in this study.

1. At screening, is between 18 and 80 years of age, both inclusive.
2. Have a documented diagnosis of congenital AATD with an allelic combination of ZZ, SZ, Z(null), (null)(null), S(null), or "at-risk" alleles (subjects with "at-risk" alleles must be individually evaluated for eligibility by the Medical Monitor). If the genotype has yet to be documented, a blood draw for genotyping (i.e., allelic discrimination) and phenotyping will be obtained at the Screening Visit. Note: The laboratory tests will not detect "at-risk" alleles and prior documentation must exist in the subject's medical records.
3. Have a documented pre-Alpha$_1$-PI augmentation therapy serum alpha-1 antitrypsin (AAT) level <11 µM (80 mg/dL if measured by radial immunodiffusion or 50 mg/dL if measured by nephelometry). Pre-Alpha$_1$-PI augmentation therapy AAT level must be documented in the subject's medical history/records.
4. Subjects may be naïve to Alpha1-PI augmentation therapy or may be currently receiving Alpha$_1$-PI augmentation therapy or received Alpha$_1$-PI augmentation therapy within the past. If the subject is currently receiving Alpha$_1$-PI augmentation therapy of any kind, he/she must be willing to discontinue that treatment for at least 25 days prior to the Week 1 (Baseline) Visit and remain off any kind of Alpha$_1$-PI treatment, other than the IPs for this study, while participating in the study.
5. At the Screening Visit, have a post-bronchodilator forced expiratory volume (FEV_1) ≥30% and <80% of predicted and FEV_1/forced vital capacity (FVC) <70% (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II or III).
6. Willing and able to provide informed consent.

Main Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Have had a moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation during the 4 weeks before the Week 1 (Baseline) Visit.
2. Have history of lung or liver transplant.

3. Have any lung surgery during the past 2 years (excluding lung biopsy).
4. At screening, have elevated liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) equal to or greater than 2.5 times the upper limit of normal (ULN).
5. Have severe concomitant disease (e.g., congestive heart failure, clinically significant pulmonary fibrosis, malignant disease [except for skin cancers other than melanoma], history of acute hypersensitivity pneumonitis reaction, or current chronic hypersensitivity pneumonitis).
6. Females who are pregnant, breastfeeding or, if of child-bearing potential, unwilling to practice a highly effective method of contraception (oral, injectable, or implanted hormonal methods of contraception, placement of an intrauterine device (IUD) or intrauterine system (IUS), condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence*) throughout the study.

   *True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
7. Have known previous infection with or clinical signs and symptoms consistent with current infection of Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), or Human Immunodeficiency Virus (HIV).
8. Have smoked during the past 6 months or a positive urine cotinine test at the Screening Visit that is due to smoking.
9. Participate in another IP study within one month prior to the Week 1 (Baseline) Visit.
10. Have history of anaphylaxis or severe systemic response to any plasma-derived Alpha1-PI preparation or other blood product(s).
11. Use systemic steroids above a stable dose equivalent to 5 mg/day prednisone (i.e., 10 mg every 2 days) within the 4 weeks prior to the Week 1 (Baseline) Visit (Note: inhaled steroids are not considered systemic steroids). It is recommended to maintain the same dose throughout the study.
12. Use systemic or aerosolized antibiotics for a chronic COPD exacerbation within the 4 weeks prior to the Week 1 (Baseline) Visit.
13. Have known selective or severe Immunoglobulin A (IgA) deficiency.
14. Subjects who cannot give independent informed consent (example: intellectual disability or cognitive disability).
15. In the opinion of the investigator, the subject may have compliance problems with the protocol and the procedures of the protocol.

Test Product, Dose and Mode of Administration:

Alpha-1 15% is a new alanine-stabilized, liquid formulation of human plasma-derived Alpha1-PI, 15% solution, for SC administration. The Alpha-1 15% manufacturing process is the same as that for a commercial product, Liquid Alpha1-PI, with additional concentration and purification steps to achieve a final protein formulation of at least 150 mg/mL (15% [w/v]).

Alpha-1 15% is supplied in 10 mL glass vials with 20 mm Latex-Free stoppers as a sterile, stable solution of Alpha$_1$-PI. Each vial of Alpha-1 15% contains the labeled amount of functionally active (potency) Alpha1-PI in milligrams per vial (approximately 1000 mg of functionally active Alpha$_1$-PI per vial). Alpha-1 15% contains no preservative and is for SC administration only.

Two doses of Alpha-1 15% are to be evaluated in this study: 72 mg/kg (Cohort 1) and 180 mg/kg (Cohort 2). The dose for Cohort 1 (72 mg/kg) was selected based on an initial dose conversion factor of 1.2 times the intravenous (IV) dose of Liquid Alpha$_1$-PI: 60 mg/kg. The dose for Cohort 2 (180 mg/kg) was selected based on a dose conversion factor of 1.5 times the 120 mg/kg of Liquid Alpha$_1$-PI, to account for the lower bioavailability observed of administration via the SC route compared to the IV route.

The planned volumes and rates of SC administration will be dependent upon various factors such as the subject's weight and tolerability. The investigator is to determine the number of SC infusion sites required based on total volume to be delivered and subject comfort. The investigator is not to exceed 8 infusion sites per infusion and the minimum distance between infusion sites is recommended to be no less than 2 inches. The target infusion rate will be no greater than 25 mL/hour/site as tolerated by the subject and per investigator's discretion. A trained homecare nurse must administer all SC infusions that are administered away from the study site. Subjects are to be observed for a minimum of 60 minutes post-IP administration for safety.

Reference Therapy, Dose and Mode of Administration:

Not Applicable.

Key Study Variables:

Safety Variables:

- Adverse events (AEs), suspected adverse drug reactions (suspected ADRs, or potentially related AEs), infusion site reactions (to be reported as AEs), serious adverse events (SAEs), and AEs and SAEs leading to discontinuation
- COPD exacerbations
- Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR], and temperature [T])
- Pulmonary function tests (PFTs):
  - FEV_1 [absolute and predicted]
  - FVC
- Clinical laboratory parameters including:
  - Chemistry
  - Hematology
  - Urinalysis
- Immunogenicity assessments

PK Variables:

PK variables include the following single-dose PK parameters of Alpha$_1$-PI, following the Single-Dose Week 1 Visit, measured using both antigenic content and functional activity assays:

- AUC of Alpha$_1$-PI from time 0 (pre-dose) to time of last quantifiable concentration (AUC_{0-t})
- AUC of Alpha$_1$-PI from time 0 (pre-dose) extrapolated to infinite time ($AUC_{0-\infty}$)
- Percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{ex}$)
- AUC of Alpha$_1$-PI from time 0 to 7 days ($AUC_{0-7\ days}$)
- Maximum concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Clearance (CL)
- Terminal half-life ($t_{1/2}$)
- Volume of distribution (V_d)
- Baseline-corrected AUC_{0-t}, $AUC_{0-\infty}$, $\%AUC_{ex}$, $AUC_{0-7\ days}$, C_{max}, CL, $t_{1/2}$, and V_d, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1)

In addition, PK variables include the following steady-state PK parameters of Alpha$_1$-PI, following the last repeat dose at Repeat-Dose Week 8, measured using both antigenic content and functional activity assays:

- Steady-state AUC of Alpha$_1$-PI over the weekly dosing interval (from 0 to 7 days) ($AUC_{0-7\ days}$)
- Steady-state mean trough Alpha$_1$-PI level, calculated as the average value of the trough measurements obtained at Repeat-Dose Weeks 6, 7, 8, and 9.
- C_{max}
- t_{max}
- CL
- $t_{1/2}$
- V_d
- Accumulation ratio, calculated as $AUC_{0-7\ days}$ following repeat-dose divided by $AUC_{0-7\ days}$ following single-dose.
- Time-invariance ratio, calculated as $AUC_{0-7\ days}$ following repeat-dose divided by $AUC_{0-\infty}$ following single-dose.
- Baseline-corrected $AUC_{0-7\ days}$, mean trough, C_{max}, CL, $t_{1/2}$, V_d, accumulation ratio, and time-invariance ratio, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1)

<u>Exploratory Variable:</u>

- Assessment of subject satisfaction with SC treatment via a written questionnaire following Treatment Period 2

Study Assessments and Procedures:

A complete schedule of study procedures and events are located in Appendix 1.

The entire duration of the study is approximately 668 days. Each cohort will consist of an up to 30-day Screening Phase, a 7-day Treatment Period 1 (Single Dose), a 21-day Washout / Serial PK Phase, an up to 18 months of a Single-Dose Data Evaluation Phase, a 56-day Treatment Period 2 (Repeat Dosing), and 7-day off-treatment Follow-up Phase.

Statistical Methods:

In general, the single-dose and repeat-dose SC regimens at the same dose level will be considered different treatment groups in data analyses. Repeat weekly IV infusions of 60 mg/kg or 120 mg/kg Liquid Alpha$_1$-PI will be additional treatment groups of interest in this study.

Safety Analyses

Safety analyses will be performed on the safety population. Safety analyses will be addressed by listing and tabulation of AEs (including suspected ADRs and ARs), infusion site reactions (to be reported as AEs), COPD exacerbations, laboratory tests, PFTs, vital signs, and physical assessments. Data will be summarized using descriptive analyses and treatment comparisons will be based on review of descriptive statistics.

Pharmacokinetic Analyses

PK parameters will be calculated using non-compartmental methods.

The single-dose PK parameters of Alpha$_1$-PI of Alpha-1 15% in subjects with AATD will be evaluated. The PK profiles of Alpha$_1$-PI following the single dose at Single-Dose Week 1 will be characterized by PK parameters, including $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $\%AUC_{ex}$, $AUC_{0\text{-}7\ days}$, C_{max}, t_{max}, $t_{1/2}$, CL, and V_d, based on Alpha$_1$-PI concentrations as measured by antigenic content as well as functional activity assays.

In addition, the steady-state PK parameters of Alpha$_1$-PI from weekly SC administration of Alpha-1 15% in subjects with AATD will be evaluated. The PK profiles of Alpha$_1$-PI following the last repeat dose at Repeat-Dose Week 8 will be characterized by PK parameters, including $AUC_{0\text{-}7\ days}$, C_{max}, t_{max}, $t_{1/2}$, CL, V_d, accumulation ratio, and time-invariance ratio, based on Alpha$_1$-PI concentrations as measured by antigenic content as well as functional activity assays. Mean trough will be calculated as the average value of the trough Alpha$_1$-PI concentrations measured at Repeat-Dose Weeks 6, 7, 8 and 9 (Final Visit).

If the dosing interval (τ) for the repeat-dose SC regimen is different from weekly (i.e., 7 days), the calculation of mean trough above will be adjusted to use appropriate trough samples only, and $AUC_{0\text{-}\tau}$ will be calculated in place of $AUC_{0\text{-}7\ days}$.

For all single-dose and repeat-dose SC PK parameters, except t_{max}, the baseline-corrected values will also be calculated, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1).

Alpha$_1$-PI concentrations at each time point and all PK parameters will be listed and summarized by treatment using descriptive statistics including n, mean, standard deviation

(SD), percent coefficient of variation (%CV), median, minimum, and maximum. Geometric mean and 90% confidence interval (CI) for the geometric mean will also be calculated for all PK parameters (except t_{max}). Data listing will include the $Alpha_1$-PI concentrations (both antigenic content and functional activity assays) at each time point as well as the corrected concentrations where the correction is performed by subtracting the Single-Dose Week 5 measurements (after 4-week washout following the end of dosing at Single-Dose Week 1) from the uncorrected concentrations at each time point.

Dose proportionality will be separately assessed for single-dose and repeat-dose SC administrations by comparing dose-normalized SC PK parameters between the 72 mg/kg and 180 mg/kg dose levels.

The impact of the volume and duration of infusion on the PK endpoints following SC administration will be evaluated by using a linear regression model fitting natural log-transformed SC PK parameters as the response variable and volume and duration of infusion as the explanatory variables.

Determination of Sample Size

No formal power/sample size calculations were performed. The sample size for each cohort is primarily based on feasibility. A sample size of 8 Alpha-1 15% subjects per cohort is deemed sufficient to address the safety and PK objectives of this early phase, dose escalation study.

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GLOSSARY AND ABBREVIATIONS

AAT	Alpha-1 antitrypsin
AATD	$Alpha_1$-antitrypsin deficiency
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
$Alpha_1$-PI	$Alpha_1$-Proteinase Inhibitor
Alpha-1 15%	$Alpha_1$-Proteinase Inhibitor Subcutaneous (Human) 15%
ALT	Alanine aminotransferase
AR	Adverse reaction
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from time 0 (pre-dose) extrapolated to infinite time
AUC_{0-t}	Area under the curve from time 0 (pre-dose) to time of last quantifiable concentration
B19V	Parvovirus B19
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLTs	Dose limiting toxicities
EC	Ethics Committee
eCRF	Electronic case report form
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH GCP	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice
IgA	Immunoglobulin A
IgG	Immunoglobulin G

IgM	Immunoglobulin M
iSRC	Internal Safety Review Committee
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
Liquid Alpha$_1$-PI	Liquid Alpha$_1$ Proteinase Inhibitor (Human)
LSM	Least square mean
MedDRA	Medical Dictionary for Regulatory Activities
NAT	Nucleic acid amplification technology
NE	Neutrophil elastase
NOAEL	No-observed-adverse-effect level
PFT	Pulmonary function test
PK	Pharmacokinetic
RBC	Red blood cell
RD	Repeat-dose
RD-SC	Repeat-dose subcutaneous
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SD-SC	Single-dose subcutaneous
T	Temperature
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach C_{max}
$t_{1/2}$	Terminal half-life
τ	Dosing interval
ULN	Upper limit of normal
US	United States
V_d	Volume of distribution
WBC	White blood cell
%AUC_{ex}	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
%CV	Percent coefficient of variation

1 GENERAL INFORMATION

Protocol title and other key study information are provided on the title page. Information regarding additional key personnel and organizations involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the Sponsor and at the investigator sites within the study reference manual/file.

Investigators and staff will receive training either via an investigator's meeting or other appropriate training session(s).

2 BACKGROUND INFORMATION

This is a multi-center, single-dose and repeat-dose over eight weeks, sequential cohort study to evaluate safety and tolerability as well as pharmacokinetics (PK) of two different doses of Alpha$_1$-Proteinase Inhibitor Subcutaneous (Human) 15% (Alpha-1 15%) administered subcutaneously in subjects with Alpha$_1$-Antitrypsin Deficiency (AATD).

In addition to the information provided below, please also refer to the Investigator's Brochure (IB) and any additional data supplied by the Sponsor.

2.1 Name and Description of the Investigational Product(s)

Alpha-1 15% is a new alanine-stabilized, liquid formulation of human plasma-derived Alpha$_1$-PI, 15% solution, for subcutaneous (SC) administration. The Alpha-1 15% manufacturing process is the same as that for an approved product, Liquid Alpha$_1$ Proteinase Inhibitor (Human) (Liquid Alpha$_1$-PI), with additional concentration and purification steps to achieve a final protein formulation of at least 150 mg/mL (15% [w/v]).

Prolastin®-C Liquid or Liquid Alpha$_1$-PI, the licensed comparator, is Grifols's liquid drug formulation of the active drug substance Alpha$_1$-PI (human). Liquid Alpha$_1$-PI is a sterile, stable, liquid preparation of purified human Alpha$_1$-PI prepared from pooled human plasma by modification and refinements of the cold ethanol fractionation method of Cohn (Cohn, 1946; Cohn, 1950).

See Section 4.4 Study Treatments for detail.

In addition to the information provided below, please also refer to the IBs (Alpha-1 15% IB; Liquid Alpha-1 IB) and any additional data supplied by the Sponsor.

2.2 Relevant Findings from Nonclinical and Clinical Trials

This is the first study of Alpha-1 15% in humans. The nonclinical safety profile of Alpha-1 15% administered by the SC route is similar to Grifols's marketed product Liquid Alpha$_1$-PI administered intravenously. The SC dose level of Alpha-1 15% planned in this study was initially selected to be 1.2 times the intravenous (IV) dose of Liquid Alpha$_1$-PI for Cohort 1; this multiplier for Cohort 1 was selected based on nonclinical PK data. For Cohort 2 the dose conversion factor has been revised to 1.5 times the IV dose of Liquid Alpha1-PI based on preliminary human PK data from Cohort 1. This modification of dose conversion factor was

performed to achieve a comparable systemic exposure of Alpha-1 PI following SC dosing of Alpha-1 15% and IV dosing of Liquid Alpha$_1$-PI.

2.2.1 Summary of Nonclinical Findings

Nonclinical PK studies in both Sprague Dawley rats and New Zealand White rabbits support linear plasma PK over a dose range of 60-600 mg/kg. Further, an SC dose multiplier of 1.2 times (mg/kg basis) to reach IV equivalent area-under-curve in plasma was established in the rabbit model.

The safety profile of Alpha-1 15% was examined in Sprague Dawley rats and New Zealand White rabbits. Dose levels of up to 10 times the current clinical dose were investigated in single dose toxicity studies; levels of up to 4 times were investigated in repeated dose toxicity studies (5-consecutive daily doses). There were no adverse effects related to Alpha-1 15% or its vehicle following single or repeated SC administration at all doses tested in either test species. The no-observed-adverse-effect level (NOAEL) was considered to be the highest dose levels tested in both species: 720 mg/kg in single-dose toxicity studies and 280 mg/kg/day for the repeated dose toxicity studies. Lastly, no new antigenic epitopes unique to Alpha-1 15% were detected in comparison to Liquid Alpha$_1$-PI in a rabbit model of neoantigenicity.

2.2.2 Liquid Alpha$_1$-PI Clinical Data

This study is the first clinical trial of Alpha-1 15% in human; therefore, there are no clinical data yet available. The reference therapy Liquid Alpha$_1$-PI in this study is a commercial product. The Alpha-1 15% manufacturing process is the same as that for Liquid Alpha$_1$-PI, with the additional concentration and purification steps to achieve a final protein formulation of at least 150 mg/mL (15% [w/v]).

Study GTI1402 was a multicenter, randomized, double-blind, crossover study to assess the safety, immunogenicity, and PK of weekly infusions of Liquid Alpha$_1$-PI 60 mg/kg compared to weekly infusions of Prolastin®-C 60 mg/kg in 32 subjects with AATD (Barker, 2017). Subjects received a total of 16 blinded, weekly IV infusions of investigational products (IPs) (8 weekly infusions of Liquid Alpha$_1$-PI and 8 weekly infusions of Prolastin-C). The order of the infusions of the IPs depended on the treatment sequence the subjects were randomized into:

- Treatment sequence 1: 8 weekly infusions of 60 mg/kg of Liquid Alpha$_1$-PI followed by 8 weekly IV infusions of 60 mg/kg of Prolastin-C
- Treatment sequence 2: 8 weekly IV infusions of 60 mg/kg of Prolastin-C followed by 8 weekly infusions of 60 mg/kg of Liquid Alpha$_1$-PI

Bioequivalence of the 2 treatments was demonstrated based on the statistical analysis of area under the curve concentrations ($AUC_{0\text{-}7\ days}$) (antigenic content). The results showed that the overall 90% confidence interval (CI) for the geometric least square mean (LSM) ratio, Liquid Alpha$_1$-PI/Prolastin-C, of the $AUC_{0\text{-}7\ days}$ falls within the range of 0.80 to 1.25, an acceptable criterion for concluding bioequivalence, thus demonstrating that weekly IV infusion of Liquid Alpha$_1$-PI 60 mg/kg produces an AUC of serum Alpha$_1$-PI that is bioequivalent to that produced by weekly infusion of Prolastin-C 60 mg/kg. The key PK parameters for

Liquid Alpha$_1$-PI and Prolastin-C in the GTI1402 study were similar to those observed in the SPARK study.

2.2.3 Weekly Infusions of 120 mg/kg Prolastin-C Compared to 60 mg/kg Prolastin-C

The SPARK study was a multicenter, randomized, double-blind, crossover study to assess the safety and PK of weekly infusions of 120 mg/kg of Prolastin-C compared to 60 mg/kg weekly infusions of Prolastin-C in 30 subjects with AATD (Campos, 2013). Subjects received a total of 16 blinded, weekly IV infusions of either 60 mg/kg or 120 mg/kg of Prolastin-C. The order of the infusions of the IPs depended on the treatment sequence the subjects were randomized into:

- Treatment sequence 1: 60 mg/kg weekly infusion of Prolastin-C for 8 weeks and then cross over to 120 mg/kg weekly infusion of Prolastin-C for 8 weeks for a total of 16 weeks of treatment
- Treatment sequence 2: 120 mg/kg weekly infusion of Prolastin-C for 8 weeks and then cross over to 60 mg/kg weekly infusion of Prolastin-C for 8 weeks for a total of 16 weeks of treatment

The results of the SPARK study showed that both doses of Prolastin-C administered weekly were safe and well tolerated. The weekly dose of 120 mg/kg Prolastin-C provided an average mean trough of Alpha$_1$-PI (27.7 µM) that falls within the reported range of Alpha$_1$-PI serum levels in normal, non-AATD individuals. Additionally, the steady-state serum concentrations of Prolastin-C were dose-proportional between the 60 mg/kg and the 120 mg/kg doses.

2.3 Known and Potential Risks and Benefits to Human Subjects

Alpha$_1$-antitrypsin deficiency symptoms may not improve and could even worsen while taking part in this study.

Individuals with selective immunoglobulin A (IgA) deficiency (a disorder where patients have low or missing blood levels of a special protein called IgA) should not receive the study drug since people with this condition may experience severe reactions, including anaphylaxis (a severe allergic reaction), to IgA which may be present in the Alpha$_1$-PI preparation.

True allergic reactions to plasma-derived Alpha$_1$-PI preparations may occur in patients with or without documented prior histories of severe allergic reactions to blood products. Very rarely, an allergic reaction may occur in patients with no prior history of severe allergic reactions to plasma-derived Alpha$_1$-PI treatment.

Both Alpha-1 15% and Liquid Alpha$_1$-PI are prepared from human plasma obtained from healthy donors. For products of biological origin, the presence of infectious agents cannot be totally excluded. However, in the case of products prepared from human plasma, the risk is reduced by: 1) epidemiological controls on the donor population and selection of individual donors by a medical interview; 2) screening of individual donations and plasma pools for viral infection markers; and 3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

The benefit for taking part in this study is to learn more about the Alpha-1 15% study drug and to allow a more convenient and flexible approach to dosing with the SC route of administration versus IV administration. SC administration will allow the patient to dose in their home environment and not have to tend to site visits weekly. SC administration may yield benefit in providing flexibility in the treatment regimen and stability in trough concentrations of serum Alpha$_1$-antitrypsin levels (Chotirmall, 2015).

2.4 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s)

2.4.1 Administration of Investigational Products

In this study, 72 mg/kg (Cohort 1) or 180 mg/kg (Cohort 2) of Alpha-1 15% will be subcutaneously administered weekly in subjects with AATD. During the Single-Dose Data Evaluation phase, two doses of Liquid Alpha$_1$-PI (60 mg/kg [Cohort 1] and 120 mg/kg [Cohort 2]) will be intravenously administered weekly in subjects with AATD.

2.4.2 Justification for Selection of Doses/Timing of Investigational Products

The serum level of Alpha$_1$-PI in normal individuals ranges from approximately 20 to 53 µM (McElvaney, 1997) and the historical serum Alpha1-PI therapeutic target trough level of 11 µM was proposed as a "protective threshold" (Gadek, 1981; Gadek, 1983). Subsequently, it was demonstrated that augmentation with 60 mg/kg Alpha1-PI administered by weekly IV infusions consistently achieved trough serum Alpha1-PI concentrations above 11 µM (Wewers, 1987). In two previous clinical studies, the steady-state mean trough concentration of Alpha1-PI following weekly doses of 60 mg/kg Prolastin-C was above the historical "protective threshold" of 11 µM in all subjects (Campos, 2013; Stocks, 2010).

Additionally, Prolastin-C Liquid (Liquid Alpha$_1$-PI) is the first United States (US) approved liquid formulation at the recommended dose of 60 mg/kg administered weekly via IV for the indications of chronic augmentation and maintenance therapy for adults with emphysema because of an Alpha$_1$-PI heredity deficiency (Prolastin®-C Liquid [US Package Insert]). Bioequivalence was demonstrated in a clinical trial comparing Liquid Alpha1-PI 60 mg/kg/wk to Lyophilized Alpha1-PI 60 g/kg/wk (Barker, 2017).

Other dosage regimens of 120 mg/kg IV every 2 weeks (Barker, 1997) and 240 mg/kg IV monthly (Barker, 1994) increased alpha$_1$-antitrypsin (AAT) serum levels above the protective threshold for most of the time; however, in the majority of the patients, levels fell below 11 µM during the last few days before the next infusion, which suggested that with a serum half-life of less than 5 days (Wewers, 1987) weekly infusion is the preferable treatment regimen. In the SPARK study (SPARK, 2012), the weekly 120 mg/kg dose of Alpha$_1$-PI provided an average mean trough of Alpha$_1$-PI (27.7 µM) that was within the normal range. This study also reported that weekly infusions of Alpha$_1$-PI at 120 mg/kg is safe and well-tolerated.

The initial dose conversion of 1.2 from IV to SC administration for Cohort 1 is based on nonclinical study findings (Section 2.2); the dose conversion factor for Cohort 2 has been revised from 1.2 to 1.5 for IV to SC administration based on preliminary PK data from Cohort 1 in order to achieve comparable systemic exposure. This modification of dose

conversion factor was performed to achieve a comparable systemic exposure of Alpha-1 PI following SC dosing of Alpha-1 15% and IV dosing of Liquid Alpha$_1$-PI.

2.4.3 Study Rationale

Alpha-1 15% is a new alanine-stabilized, liquid formulation of human plasma-derived Alpha$_1$-PI, 15% solution, for SC administration. The Alpha-1 15% manufacturing process is the same as that for a commercial product, Liquid Alpha$_1$-PI, with additional concentration and purification steps to achieve a final protein formulation of at least 150 mg/mL (15% [w/v]).

Unlike lyophilized formulations of Alpha$_1$-PI, Alpha-1 15% does not require reconstitution or optional filtration steps during its preparation for use; thus, the potential for reconstitution errors is eliminated, and preparation time is shortened. Additionally, a SC formulation may allow for at-home administration. A higher concentrated Alpha$_1$-PI formulation available for SC administration is desirable by caregivers and patients due to its relative ease of preparation compared to lyophilized formulations of Alpha$_1$-PI, less volume required for dosing with equivalent potency, no need to visit a hospital or infusion center, and an alternative that would be more conducive with activities of daily living. Thus, Grifols is conducting a multicenter, single-dose and repeat-dose over eight weeks, sequential cohort study to evaluate safety and tolerability as well as pharmacokinetics of two different doses of alpha$_1$-proteinase inhibitor subcutaneous (human) 15% administered subcutaneously in subjects with alpha$_1$-antitrypsin deficiency.

While there are abundant data supportive of a treatment effect of Alpha1-PI in standard dosing (i.e., 60 mg/kg/week) for patients with AATD, the question of whether higher doses of Alpha$_1$-PI would be more effective in slowing and/or preventing emphysema progression remains unanswered. The SPARK study (NCT01213043) with Prolastin-C was undertaken to provide preliminary information on the safety of a higher dose regimen, 120 mg/kg weekly. Results from previous studies of IV Alpha$_1$-PI augmentation therapy at dose regimens other than 60 mg/kg weekly, including 120 mg/kg biweekly, 180 mg/kg triweekly, and 240 mg/kg every 4 weeks or monthly (Barker, 1997; Barker, 1994; Hubbard, 1988; Dirksen, 1999), have indicated that such higher dose regimens are safe and well tolerated. The results of the SPARK study indicated that both 60 mg/kg and 120 mg/kg doses of Alpha$_1$-PI administered weekly were safe and well tolerated, and further investigation of the weekly dose of 120 mg/kg Alpha$_1$-PI which Grifols is currently conducting as a large multinational study called SPARTA.

2.5 Compliance Statement

This study will be conducted under the conditions described in this protocol and in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and all applicable regulatory requirements.

2.6 Study Population

The study population will consist of subjects with a diagnosis of AATD, both male and female, between the ages of 18 and 80 years, with clinical evidence of pulmonary emphysema per the investigator's judgement. Subjects must meet all the inclusion criteria and none of the exclusion criteria at the screening visit to be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site, prior to study treatment administration.

2.7 Relevant Data and Literature Review

2.7.1 Alpha$_1$-Antitrypsin Deficiency

Alpha$_1$-antitrypsin deficiency is a genetic disorder in which mutations of the SERPINA1 gene (a member of the SERPIN, serine protease inhibitor gene family) lead to a reduced serum level of the serine protease inhibitor called Alpha$_1$-proteinase inhibitor (Alpha$_1$-PI) or, historically, Alpha$_1$-antitrypsin. Alpha$_1$-antitrypsin deficiency manifests clinically as chronic obstructive pulmonary disease (COPD), pulmonary emphysema, and liver cirrhosis (Mulgrew, 2007; Köhnlein, 2008; Fregonese, 2008).

Within the lung airways, neutrophil recruitment is thought to be an important component of continuing inflammation and progression of COPD (Woolhouse, 2002). When neutrophils phagocytize, an array of enzymes, including proteases such as neutrophil elastase (NE) may destroy tissue. Alpha$_1$-PI is the most abundant circulating tissue inhibitor of NE (Carrell, 1982; Travis, 1988) and constitutes an important part of the lung's protective protease inhibitory shield and maintenance of the normal protease:antiprotease balance in the lungs (Gadek, 1981). Several incidents of increased concentrations of NE and neutrophils in the lungs of AATD patients have been noted (Woolhouse, 2002; Rouhani, 2000; Wencker, 2005; Morrison, 1987). In AATD there appears to be an inadequate protective protease inhibitory shield (Gadek, 1981; Janoff, 1985; Hubbard, 1991), a disruption of the normal protease:antiprotease balance (Gadek, 1981; American Thoracic Society/ European Respiratory Society Statement, 2003; Crystal, 1990) and an unopposed action of NE leading to destruction of lung matrix and, over time, to the development of emphysema (Gadek, 1981; Janoff, 1985; Hubbard, 1991; Janoff, 1977; Senior, 1977; Stockley, 2009).

2.7.2 Alpha$_1$-PI Augmentation Therapy

Augmentation therapy with IV Alpha$_1$-PI is administered in patients with AATD to increase the low serum concentrations in this patient population. This usage is intended to bolster the protective protease inhibitory shield against increased numbers of lung neutrophils releasing increased concentrations of NE, leading to a corrected protease:antiprotease imbalance (Gadek, 1983; Wewers, 1987, Crystal, 1990, Gadek, 1981). The restored antiprotease shield then protects the lung from elastolytic damage and slows or prevents the development of pulmonary emphysema (Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998; Seersholm, 1997).

Administration of IV augmentation Alpha$_1$-PI therapy weekly is currently the only approved route of administration and treatment regimen, however SC administration may yield benefit

in providing flexibility in the treatment regimen and stability in trough concentrations of serum Alpha$_1$-antitrypsin levels (Chotirmall, 2015). In 2001, use of augmentation therapy accounted for over half of the costs for an individual with AATD, while the other major cost contributors included hospitalizations and physician visits. The average annual cost for a patient on augmentation therapy was greater than $40K/year (Chotirmall, 2015). A separate study analyzed the average medical costs of patients on augmentation therapy from 1993 through 2015, finding that the average cost per year was over $127K, with greater than $25K/year attributed to physician visits, emergency department visits, and inpatient stays (Sieluk, 2019). Cost-effectiveness of augmentation therapy needs to be improved. Subcutaneous administration of augmentation therapy will provide flexibility in treatment regimen, as patients may be able to self-administer Alpha-1 15% at home, minimizing costly factors such as physician visits.

In addition to the information provided here, please also refer to the Alpha-1 15% and Liquid Alpha$_1$-PI IBs and any additional data supplied by the Sponsor (Alpha-1 15% IB; Liquid Alpha-1 IB).

3 STUDY OBJECTIVES

3.1 Primary Objective

3.1.1 Primary Objective

To evaluate the safety and tolerability of 72 mg/kg and 180 mg/kg Alpha-1 15%, administered as a single-dose SC infusion and subsequently as weekly SC infusions over 8 weeks in subjects with AATD.

3.1.2 Pharmacokinetic Objective

The PK objective is to evaluate the PK of Alpha$_1$-PI, measured using both antigenic content and functional activity assays, following a single-dose SC infusion and subsequently eight weekly SC infusions of 72 mg/kg or 180 mg/kg Alpha-1 15% in subjects with AATD.

3.1.3 Exploratory Objective

The exploratory objective of this study is to assess subject satisfaction with SC treatment following eight weeks of SC doses of 72 mg/kg or 180 mg/kg Alpha-1 15% in subjects with AATD.

An additional exploratory PK objective is to evaluate the PK of Alpha$_1$-PI, measured using both antigenic content and functional activity assays, following 8 weekly IV infusions of 60 mg/kg or 120 mg/kg Liquid Alpha$_1$-PI in subjects with AATD.

4 STUDY DESIGN

4.1 Primary Endpoints

- Adverse events (AEs), suspected adverse drug reactions (suspected ADRs, or potentially related AEs), infusion site reactions (to be reported as AEs), serious adverse events (SAEs), and AEs and SAEs leading to discontinuation
- COPD exacerbations
- Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR], and temperature [T])
- Pulmonary function tests (PFTs):
    - Forced Expiratory Volume in 1 second (FEV_1) [absolute and predicted]
    - Forced Vital Capacity (FVC)
- Clinical laboratory parameters including:
    - Chemistry
    - Hematology
    - Urinalysis
- Immunogenicity assessments

4.2 Study Design and Plan

This is a multi-center, single-dose and repeat-dose over 8 weeks, sequential cohort study evaluating safety and tolerability as well as PK of 2 different doses of $Alpha_1$-proteinase inhibitor SC (human) 15% administered subcutaneously as $Alpha_1$-PI augmentation in subjects with AATD.

An internal safety review committee (iSRC), comprised of impartial and independent members at least the Grifols medical monitor or qualified medical designee, pharmacovigilance, and a third individual of the study team such as someone knowledgeable in the epidemiological field or, knowledgeable in the therapeutic area, or a statistician will be established to monitor the progress and the safety of the clinical trial participants, as well as any pump related issues. The iSRC charter will outline the composition, responsibilities, schedule of the iSRC meetings, and study stopping rules. At a minimum, the iSRC will convene to review subject data, including but not limited to demographics, dosing, concomitant medications, hematology and chemistry, and adverse events to confer and document agreement that the next dose level is considered appropriate and safe.

The first Cohort will include approximately 8 subjects receiving the 72 mg/kg (Cohort 1) starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha1-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose), safety data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data

Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (60 mg/kg for Cohort 1) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 1. Following completion of Treatment Period 2 (Repeat-Dose) for subjects in Cohort 1, the iSRC will evaluate safety data prior to initiating Cohort 2 (180 mg/kg). Dosing must not commence to Cohort 2 until Grifols has provided written confirmation to the principal investigators (PI). If the iSRC determines it is safe to proceed with dose escalation, Cohort 2 will be initiated.

The second cohort will include approximately 8 subjects receiving the 180 mg/kg (Cohort 2) dose of Alpha-1 15% starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). Furthermore, enrollment into Cohort 2 will only commence once the iSRC has reviewed safety data from the entire cohort of subjects treated with 72 mg/kg. **Subjects cannot enroll into both cohorts**. To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose) phase, safety data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (120 mg/kg for Cohort 2) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) from a subset of subjects will be evaluated by the study team to determine/confirm the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 2.

Dose-limiting toxicities (DLTs) will be assessed by the investigator based on toxicity grade according to the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5.0) clinical significance and possible relationship to study drug. The DLT evaluation period for the determination of the next dose level will be in the first 7 days immediately following the first SC injection. See Section 4.6.3 for further details.

The Schedule of Study Procedures and Events table is provided in Appendix 1. The study consists of a Screening Phase, Treatment Phase, and Follow-up Phase. The overall study design is presented in Figure 4-1 (Overall Cohort Schema), Figure 4-2 (Staggering Dose Schema for Each Cohort), and Figure 4-3 (Overall Study Schema for Each Cohort).

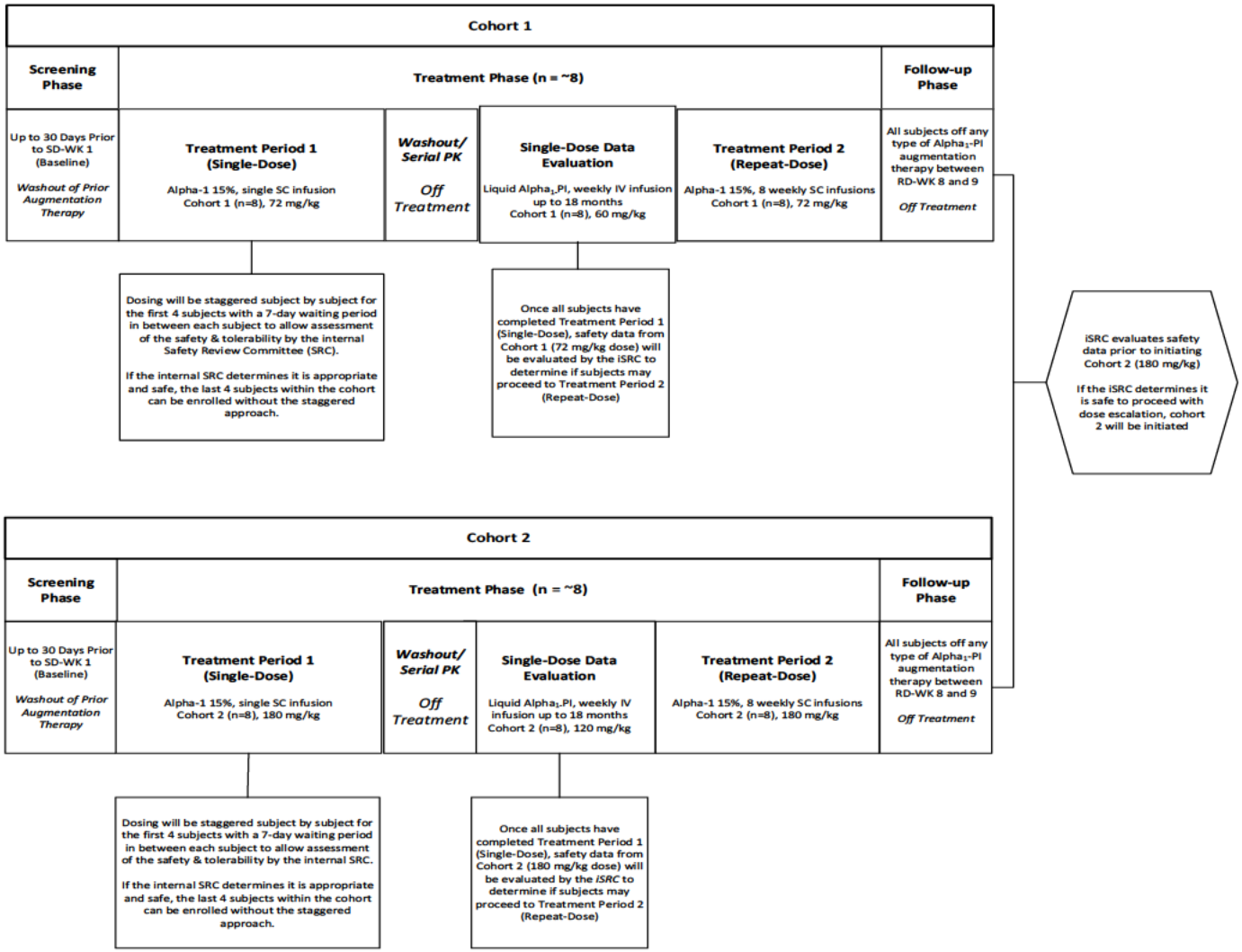


Figure 4-1 Overall Cohort Schema

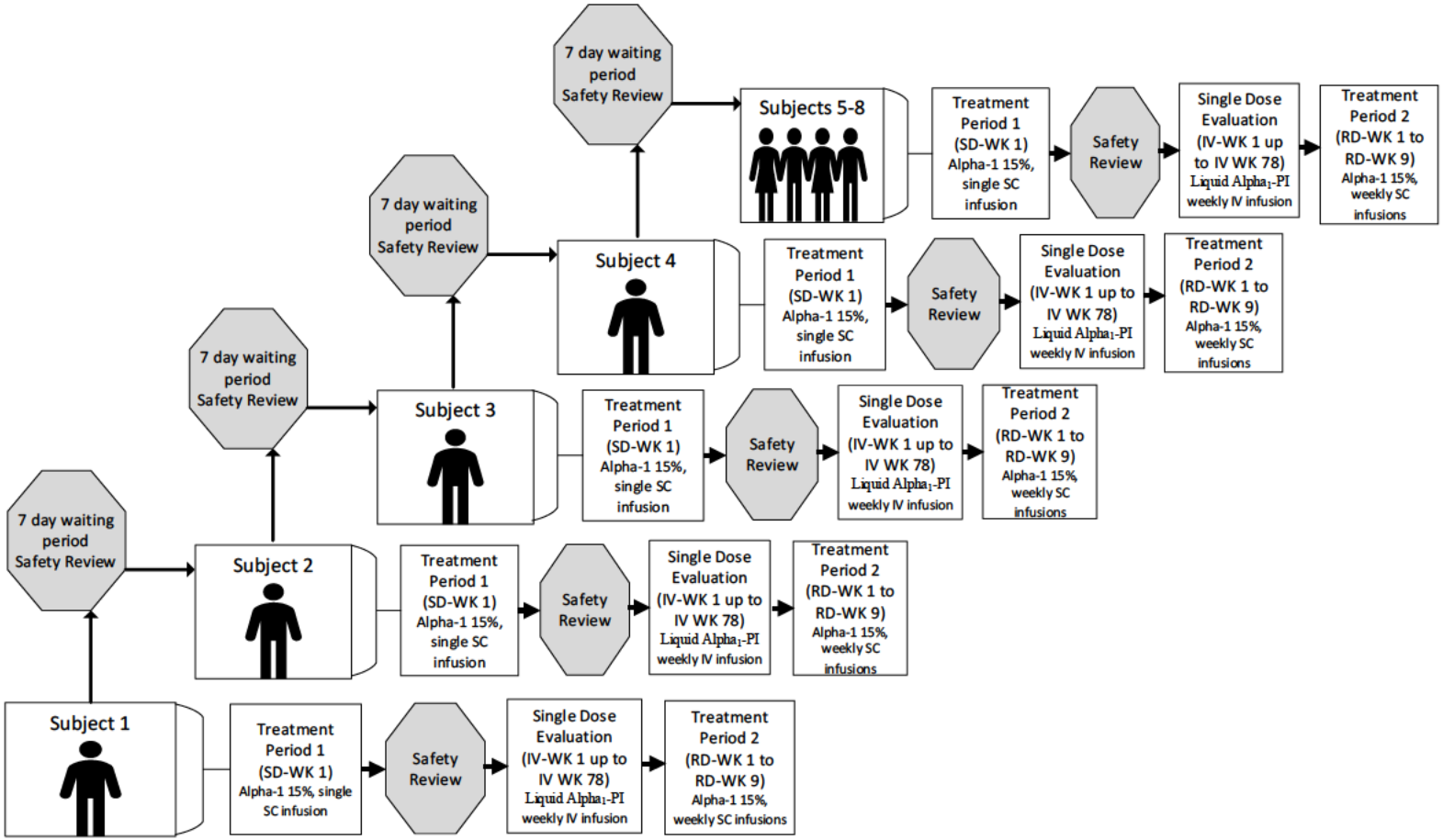
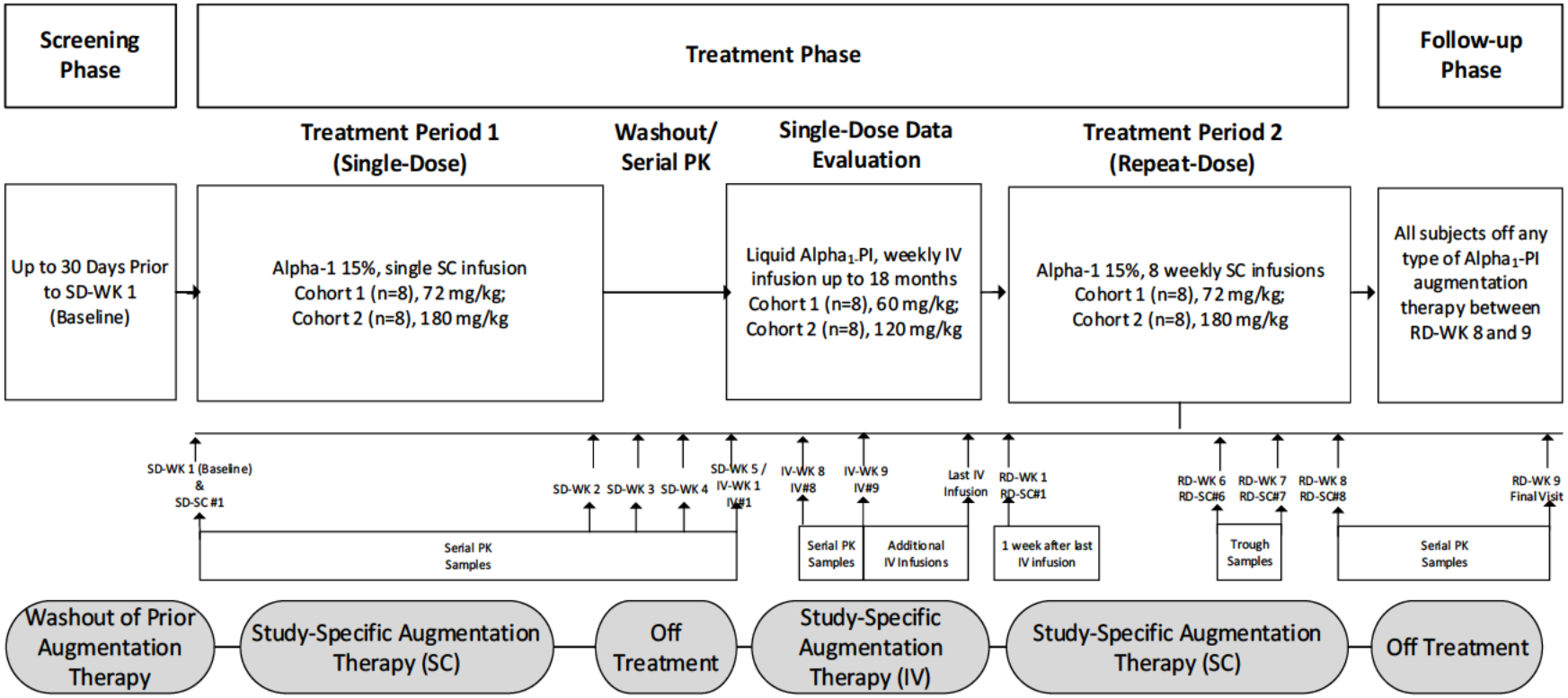


Figure 4-2 Staggering Dose Schema for Each Cohort

Each cohort will consist of an up to 30-day Screening Phase, a 7-day Treatment Period 1, a 21-day Washout / Serial PK Phase, an up to 18 months of a Single-Dose Data Evaluation Phase, a 56-day Treatment Period 2, and 7-day off-treatment Follow-up Phase. Subjects will receive their first single SC dose of investigational product (IP; Alpha-1 15%) at Single-Dose Week 1 (Baseline;). Subjects will receive their last repeat SC dose of IP at Repeat-Dose Week 8. Serial PK samples will be collected following the single dose at Single-Dose Week 1 over a 4-week period and following the last repeat dose at Repeat-Dose Week 8 over a 1-week period. Trough PK samples will be collected at steady-state during Treatment Period 2. Study visits and essential activities for each cohort are summarized in Figure 4-3.



IV: intravenous; PK: pharmacokinetic; SC: subcutaneous; SD: single-dose; RD: repeat-dose; WK: week.

NOTE: Repeat-dose SC regimens in Treatment Period 2 will be determined after reviewing single-dose safety and PK data from Treatment Period 1 and may be different from those shown in the schema. If the dosing interval (τ) for the repeat-dose SC regimen is different from weekly (i.e., 7 days), the trough and serial PK sampling schedules in Treatment Period 2 will be adjusted to allow for a full characterization of the mean trough and $AUC_{0-\tau}$. Furthermore, all subjects will have a minimum of 9 weeks of Liquid $Alpha_1$-PI before proceeding to repeat-dose SC period (Treatment Period 2).

Figure 4-3 Overall Study Schema for Each Cohort

4.3 Measures Taken to Minimize/Avoid Bias

4.3.1 Subject Numbering

Within each study site, subjects will receive a consecutive subject number upon signing informed consent to participate in the study. Subject numbers are generated beginning with the study center number (3 digits, assigned by the Sponsor) followed consecutively with a unique number for each subject (4 digits, beginning with the number "8"). For example, if the investigator's center number is 301, subject number will be 3018001, 3018002, 3018003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center. If a subject is re-screened, a different subject number will be assigned to this subject.

4.3.2 Randomization

Randomization is not applicable.

4.3.3 Blinding

Blinding is not applicable. This is an open-label study.

4.4 Study Treatments

4.4.1 Treatments to Be Administered

The IPs to be administered during this study are Alpha-1 15% and Liquid Alpha$_1$-PI.

4.4.1.1 Alpha$_1$-Proteinase Inhibitor Subcutaneous (Human) 15%

Alpha-1 15% is supplied in 10 mL glass vials with 20 mm Latex-Free stoppers as a sterile, stable solution of Alpha$_1$-PI. Each vial of Alpha-1 15% contains the labeled amount of functionally active (potency) Alpha$_1$-PI in milligrams per vial (approximately 1000 mg of functionally active Alpha$_1$-PI per vial). Alpha-1 15% contains no preservative and is for SC administration only.

Alpha-1 15% is a new alanine-stabilized, liquid formulation of human plasma-derived Alpha$_1$-PI, 15% solution, for SC administration. The Alpha-1 15% SC manufacturing process is the same as that for Liquid Alpha$_1$-PI, with additional concentration and purification steps to achieve a final protein formulation of at least 150 mg/mL (15% [w/v]).

Two doses of SC Alpha-1 15% are to be evaluated in this study: 72 mg/kg (Cohort 1) and 180 mg/kg (Cohort 2). The dose for Cohort 1 (72 mg/kg) was selected based on an initial dose conversion factor of 1.2 times the IV dose of Liquid Alpha$_1$-PI: 60 mg/kg (based on preclinical animal studies [see Section 2.2]). The dose for Cohort 2 (180 mg/kg) was selected based on a dose conversion factor of 1.5 times the 120 mg/kg of Liquid Alpha$_1$-PI, to account for the lower bioavailability observed from preliminary human PK data from Cohort 1 for administration via the SC route compared to the IV route.

4.4.1.2 Liquid Alpha$_1$-Proteinase Inhibitor (Human)

Liquid Alpha$_1$-PI is supplied in 20 mL glass vials as a sterile, stable solution of Alpha$_1$-PI. Each vial of Liquid Alpha$_1$-PI contains the labeled amount of functionally active (potency) Alpha$_1$-PI in milligrams per vial (approximately 1000 mg of functionally active Alpha$_1$-PI per vial). Liquid Alpha$_1$-PI contains no preservative. Liquid Alpha$_1$-PI is for IV administration only.

Two doses of Liquid Alpha$_1$-PI will be used in this study: 60 mg/kg weekly (the licensed dose) and 120 mg/kg weekly. Liquid Alpha IV in this study is provided between the SC single dose and repeat dose SC treatment periods in order to allow all subjects to complete the single dose portion so that safety on all subjects can be assessed prior to advancing to the repeat dose portions of the study with the SC Alpha-1 15%. Secondly the PK of the Liquid Alpha$_1$-PI IV dose of 60 mg/kg will be compared to the PK of the 72 mg/kg SC Alpha 15% and correspondingly the 120 mg/kg Liquid Alpha$_1$-PI IV will be compared to the PK of the 180 mg/kg SC Alpha 15%.

4.4.2 Labeling of Investigational Product(s)

Investigational products will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed Grifols procedures, and a copy of the labels will be made available to the study site. The pharmacist will refer to the lot-specific labeled amount of functionally active Alpha$_1$-PI in milligrams per vial (potency) when preparing the subject-specific volume for infusion with no rounding up or down of the whole vial content of product.

4.4.3 Packaging of Investigational Product(s)

Investigational products will be packaged according to the requirements of local law and legislation. Packaging text will be approved according to agreed Grifols procedures.

4.4.4 Storage of Investigational Product(s)

Investigational products should be stored at a temperature (T) from 2 to 8°C (36 to 46°F); do not freeze.

Investigational products must be stored in a secure area, accessible only to study personnel authorized by the investigator, such as the study staff responsible for the preparation and dispensing of IP. For Alpha-1 15%, IP should be stored at a subject's residence or other locations in a working refrigerator.

Details for the storage of both IPs are located in the Pharmacy Manual provided to each site.

4.5 Expected Duration of Subject Participation in the Study

Each cohort will consist of an up to 30-day Screening Phase, a 7-day Treatment Period 1, a 21-day Washout / Serial PK Phase, an up to 18 months of a Single-Dose Data Evaluation Phase, a 56-day Treatment Period 2, and 7-day off-treatment Follow-up Phase. Subjects will

receive their first SC dose of investigational product (IP; Alpha-1 15%) at Single-Dose Week 1 (Baseline). Subjects will receive their last SC dose of IP at Repeat-Dose Week 8.

4.6 Discontinuation Criteria for Individual Subjects and Study

4.6.1 Discontinuation Criteria for Individual Subjects

See Section 5.3 Subject Withdrawal Criteria

4.6.2 Premature Termination of Study/Closure of Center

The Sponsor, Institutional Review Board/Ethics Committee (IRB/EC), and/or regulatory authorities have the right to close this study or a study center, and the investigator/Sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The IRB/EC must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The investigator will retain all other documents until notification given by the Sponsor for destruction.

The reasons a study center may be closed include, but are not limited to, the following:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with ICH GCP

4.6.3 Dose-limiting Toxicities and Stopping Rules

Dose-limiting toxicities (DLT) will be assessed by the investigator based on toxicity grade according to the CTCAE v5.0, clinical significance, and possible relationship to study drug. The DLT evaluation period for the determination of the next dose level will be in the first 7 days immediately following the first SC injection.

Cohort 1 (Alpha-1 15%: 72 mg/kg SC weekly):

In Cohort 1, four subjects will be initially dosed at the 72 mg/kg Alpha-1 15% dose level. Each subject will start with single-dose and cross over to repeat-dose after a washout period and after safety is evaluated. The first four subjects will be staggered with 7 day waiting periods between each subject. If a DLT is observed in 0 or 1 of the first 4 Alpha-1 15% subjects at the initial dose level of 72 mg/kg, then 4 additional subjects will be enrolled at the same dose level. If >1 DLT is observed at any point in time in Alpha-1 15% subject(s), the iSRC will review the data to determine if dosing can continue at the 72 mg/kg dose level or if the study should be stopped. If dosing continues, an additional 4 subjects will be dosed at the 72 mg/kg dose level. Out of the approximately 8 Alpha-1 15% subjects at this dose level, if 2 or less DLTs are observed in Alpha-1 15% subject(s), then dose escalation will continue to the 180 mg/kg dose level. If >2 DLTs are observed in the approximately 8 Alpha-1 15% subjects, the iSRC will review the data to determine if dose escalation to 180 mg/kg can occur or if the study should be stopped. Upon determination of continuing to the next dose level the same rules will apply for DLT evaluation.

Cohort 2 (Alpha-1 15%: 180 mg/kg SC weekly):

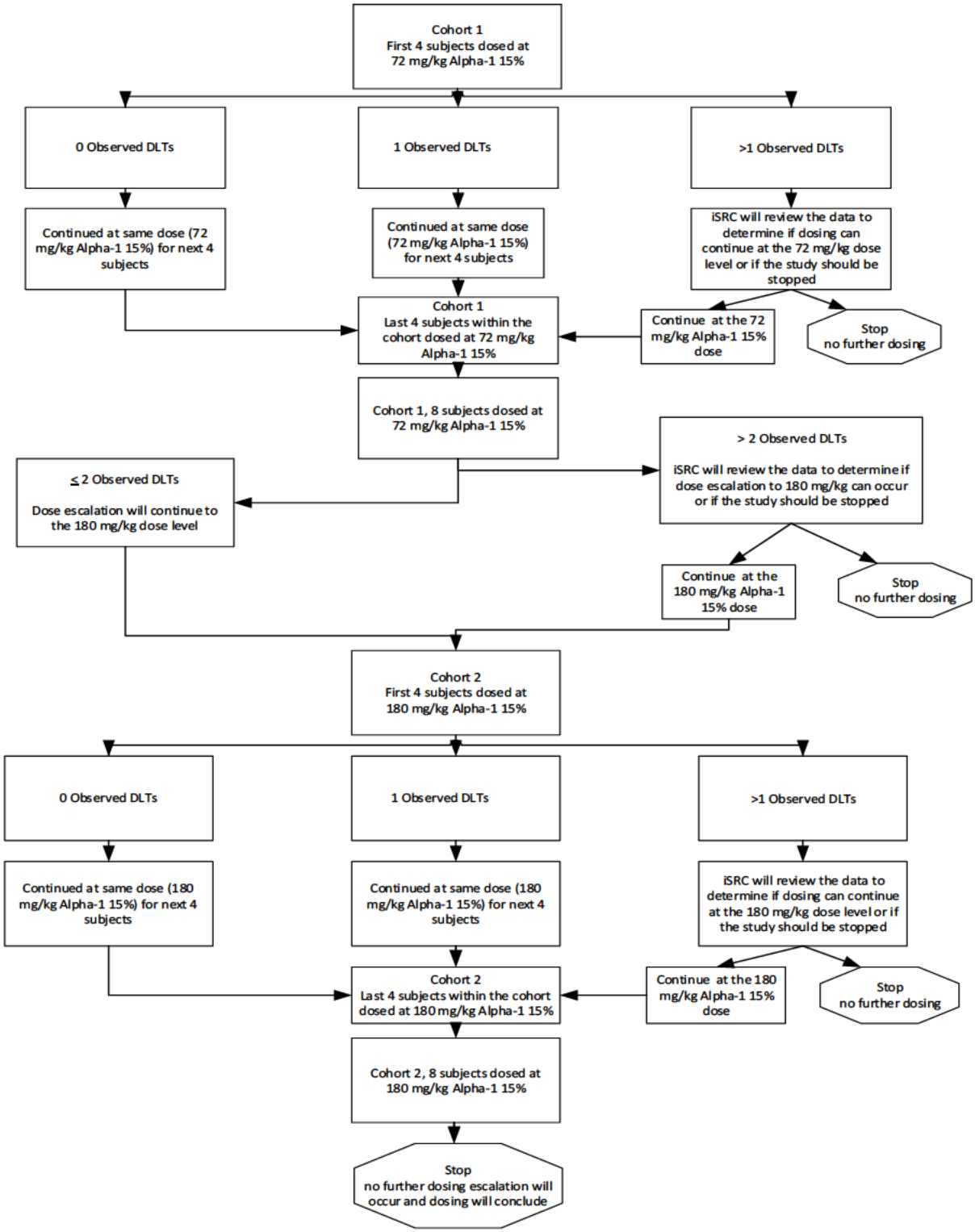
In Cohort 2, 4 subjects will be initially dosed at the 180 mg/kg Alpha-1 15% dose level. Each subject will start with single-dose, enter into the Single-Dose Data Evaluation Phase, and cross over to repeat-dose after a washout period and after safety is evaluated as follows: The first 4 subjects will be staggered with 7 day waiting periods between each subject. If a DLT is observed in 0 or 1 of the 4 Alpha-1 15% subjects at the initial dose level of 180 mg/kg, then 4 additional subjects will be enrolled at the same dose level. If >1 DLT is observed in Alpha-1 15% subject(s), the iSRC will review the data to determine if dosing can continue at the 180 mg/kg dose level or if the study should be stopped. If dosing continues, an additional 4 subjects will be dosed at the 180 mg/kg Alpha-1 15% dose level. Upon completion of dosing of subjects at this dose level, no further dosing escalation will occur, and dosing will conclude.

A DLT considered for dose escalation will be defined as any of the following occurring within 7 days of initiating SC injection of study drug that is assessed by the investigator as possibly related to Alpha-1 15%. Where applicable the event will be assessed by CTCAE v5.0.

- Grade 3 or greater edema lasting more than 4 days
- Grade 3 or greater erythema lasting more than 4 days
- Any Grade 3 or greater injection site reaction lasting more than 4 days
    - Note: The following will not be included: mild/moderate irritation, redness, and/or swelling at injection site for this assessment.

In addition to the DLT and study stopping rules, individual stopping rules that would include positive testing for immunogenicity and severe infusion site reactions causing the subject to prematurely discontinue the study will be implemented. Stopping rules will be based on safety outcomes in cases where infusion site reactions emerge at unexpectedly high or severe levels or a subject is deemed positive for immunogenicity.

The DLT schema is presented in Figure 4-4.



DLT: Dose limiting toxicities; iSRC: Internal Safety Review Committee.

Figure 4-4 Dose-Limiting Toxicities Schema

4.7 Accountability Procedures for Investigational Product(s)

Investigational product is to be used only for the study in accordance with the directions given in this protocol. The investigator, or designee such as the study pharmacist, is responsible for the distribution of the investigational product in accordance with directions given in the protocol and pharmacy manual.

The investigator is responsible for maintaining accurate records of the investigational product for his/her site. Investigational product inventory/dispensing documentation verifying the receipt, dispensing, destruction, or return must be maintained and kept current by the investigator, or designee. The inventory must be made available for inspection by the monitor. Investigational product supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to Investigational product return or destruction. Written documentation of any used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols.

4.8 Maintenance of Treatment Randomization Codes

Not applicable.

4.9 Data to be Recorded Directly on the CRFs/eCRFs

Source documents will be used to record all study-related data. Designated staff will enter the data required by the protocol into the electronic Case Report Form (eCRF) based on available source documents to support the data entries.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

Eligible participants for this study will include male or female subjects who are 18 to 80 years of age, have a diagnosis of AATD, and have clinical evidence of pulmonary emphysema per the investigator's judgment. Subjects who initially fail to meet eligibility criteria during the Screening Phase may be rescreened upon consultation with the Sponsor. Subjects who fail to meet eligibility criteria upon re-screen are screen failures and will not be eligible to participate in the study.

5.1 Inclusion Criteria

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

1. At screening, is between 18 and 80 years of age, both inclusive.
2. Have a documented diagnosis of congenital AATD with an allelic combination of ZZ, SZ, Z(null), (null)(null), S(null), or "at-risk" alleles (subjects with "at-risk" alleles must be individually evaluated for eligibility by the Medical Monitor). If the genotype has yet to be documented, a blood draw for genotyping (i.e., allelic discrimination) and phenotyping will be obtained at the Screening Visit. Note: The laboratory tests will not

detect "at-risk" alleles and prior documentation must exist in the subject's medical records.

3. Have a documented pre-Alpha$_1$-PI augmentation therapy serum AAT level <11 µM (80 mg/dL if measured by radial immunodiffusion or 50 mg/dL if measured by nephelometry). Pre-Alpha$_1$-PI augmentation therapy AAT level must be documented in the subject's medical history/records.
4. Subjects may be naïve to Alpha1-PI augmentation therapy or may be currently receiving Alpha$_1$-PI augmentation therapy or received Alpha$_1$-PI augmentation therapy in the past. If the subject is currently receiving Alpha$_1$-PI augmentation therapy of any kind, he/she must be willing to discontinue that treatment for at least 25 days prior to the Week 1 (Baseline) Visit and remain off any kind of Alpha$_1$-PI treatment, other than the IPs for this study, while participating in the study.
5. At the Screening Visit, have a post-bronchodilator FEV_1 ≥30% and <80% of predicted and FEV_1/ FVC <70% (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II or III; GOLD, 2018).
6. Willing and able to provide informed consent.

5.2 Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Have had a moderate or severe COPD exacerbation during the 4 weeks before the Week 1 (Baseline) Visit.
2. Have history of lung or liver transplant.
3. Have any lung surgery during the past 2 years (excluding lung biopsy).
4. At screening, have elevated liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) equal to or greater than 2.5 times the upper limit of normal (ULN).
5. Have severe concomitant disease (e.g., congestive heart failure, clinically significant pulmonary fibrosis, malignant disease [except for skin cancers other than melanoma], history of acute hypersensitivity pneumonitis reaction, or current chronic hypersensitivity pneumonitis).
6. Females who are pregnant, breastfeeding or, if of child-bearing potential, unwilling to practice a highly effective method of contraception (oral, injectable, or implanted hormonal methods of contraception, placement of an intrauterine device (IUD) or intrauterine system (IUS), condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence*) throughout the study.

   *True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)

7. Have known previous infection with or clinical signs and symptoms consistent with current infection of Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), or Human Immunodeficiency Virus (HIV).
8. Have smoked during the past 6 months or a positive urine cotinine test at the Screening Visit that is due to smoking.
9. Participate in another IP study within one month prior to the Week 1 (Baseline) Visit.
10. Have history of anaphylaxis or severe systemic response to any plasma-derived Alpha1-PI preparation or other blood product(s).
11. Use systemic steroids above a stable dose equivalent to 5 mg/day prednisone (i.e., 10 mg every 2 days) within the 4 weeks prior to the Week 1 (Baseline) Visit (Note: inhaled steroids are not considered systemic steroids). It is recommended to maintain the same dose throughout the study.
12. Use systemic or aerosolized antibiotics for a COPD exacerbation within the 4 weeks prior to the Week 1 (Baseline) Visit.
13. Have known selective or severe IgA deficiency.
14. Subjects who cannot give independent informed consent (example: intellectual disability or cognitive disability).
15. In the opinion of the investigator, the subject may have compliance problems with the protocol and the procedures of the protocol.

5.3 Subject Withdrawal Criteria

Subjects who receive any amount of IP and discontinue early from the study will be requested to return to have all assessments completed for the Early Withdrawal Visit as close as practical to 28 days after their last administration of the IP.

5.3.1 Screen Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment. Subjects who fail to meet eligibility criteria during screening evaluations will be considered screen failures and will not participate in the study. However, subjects who fail the first screening evaluation are allowed to be re-screened once.

If a subject is re-screened, a different subject number will be assigned to this subject. If more than 30 days has occurred between the initial screening visit and the rescreen visit, it is recommended that a new informed consent be obtained. However, timing for re-consenting is contingent upon the site's IRB.

5.3.2 Removal of Subjects

Subjects may withdraw or be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative.
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.

- At the specific request of the Sponsor.

Also, subjects must be withdrawn for the following reasons:

- Subjects with an occurrence of a concomitant disease, or any medical condition which, either because of its severity or duration or necessary change in treatment, contravenes the condition of the study or puts the patient at unnecessary risk or harm per the investigator's discretion
- Subjects with an occurrence of an AE, which in the opinion of the investigator and/or subject, requires termination of treatment
- Subjects who are noncompliant with the protocol, per the investigator's discretion
- Subjects who develop an infection with HAV, HBV, HCV, HIV or parvovirus B19 (B19V) during the study.
- Subjects who become pregnant
- Subjects who have a positive urine cotinine test due to smoking

In all cases, the reason for withdrawal must be recorded in the subject's source documentation records and in the CRF/eCRF.

5.3.3 Subject Replacement

Subjects who are enrolled and withdrawn from the study will not be replaced.

5.3.4 Follow-up of Subjects Withdrawn from Study

Subjects who receive any amount of IP and discontinue early from the study will be requested to return to have all assessments completed for the Early Withdrawal Visit as close as practical to 28 days after their last IP administration, provided that the subjects do not withdraw their consent to participate in this study.

6 TREATMENT OF SUBJECTS

See Section 4.4 for the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration.

6.1 Administration and Timing of Investigational Products for Each Subject

Enrollment will occur in two sequential cohorts of approximately 8 subjects each. The first Cohort will include approximately 8 subjects receiving the 72 mg/kg starting with a single-dose of Alpha-1 15%. Safety will be evaluated following the single-dose SC infusion prior to the subject crossing-over to the Repeat-Dose SC infusions. Likewise, safety from the 72 mg/kg treatment cohort will be evaluated by an iSRC prior to escalating to Cohort 2. Dosing must not commence to Cohort 2 until Grifols has provided written confirmation to the investigators. The second cohort will include approximately 8 subjects receiving the 180 mg/kg dose of Alpha-1 15%. Subjects cannot enroll into both cohorts. Furthermore, within each cohort dosing will be staggered subject by subject for the first 4 subjects with a

7-day waiting period in between each subject, to allow assessment of the safety and tolerability by the iSRC. If the iSRC determines it is appropriate and safe, the last 4 subjects within the cohort can be enrolled without the staggered approach.

The site pharmacist will use the subject's weight obtained at the Single-Dose Week 1 (Baseline) Visit to calculate the Alpha-1 15% SC infusion dose for Treatment Period 1, the weight obtained at the Single-Dose Week 5/Intravenous Week 1 Visit to calculate the Liquid Alpha-1 IV infusion for the Single-Dose Data Evaluation Period, and the weight obtained at the Repeat-Dose Week 1 Visit to calculate the Alpha-1 15% SC infusion dose for Treatment Period 2. The site pharmacist will use the actual lot-specific labeled amount of functionally active (potency) $Alpha_1$-PI printed on the vials of the IP with no rounding up or down on the whole vial content of the IP.

6.1.1 Treatment Period 1 for Each Cohort

The first SC infusion will be administered as a single-dose and given under supervision in the clinic. The selected pump, specifically designed for SC infusions, will be provided for individual use to each subject prior to Treatment Period 1. The exact Alpha-1 15% dose (and dose volume) administered based on the predetermined conversion factor will be documented and entered into the subject's source documentation records and eCRF.

The planned volumes and rates of SC administration will be dependent upon various factors such as the subject's weight and tolerability. The investigator is to determine the number of SC infusion sites required based on total volume to be delivered and subject comfort. The principal investigator is not to exceed 8 infusion sites per infusion and the minimum distance between infusion sites is recommended to be no less than 2 inches. The target infusion rate will be no greater than 25 mL/hour/site as tolerated by the subject and per investigator's discretion. Subjects are to be observed for a minimum of 60 minutes post-IP administration for safety.

6.1.2 Single-Dose Data Evaluation Period

For the Single-Dose Data Evaluation Period, a site pharmacist, or designee, will prepare an infusion bag of Liquid Alpha-1 (Prolastin), and subjects will receive contents of the bag via IV administration. To complete the infusion, the IV line will be flushed with 0.9% Sodium Chloride for Injection (NaCl) to ensure that the entire prepared dose of Liquid Alpha-1 (Prolastin) is infused into the subject. The infusion is considered complete only after the IV line has been flushed.

For each infusion, the total infusion volume prepared, infusion start date/time, infusion end date/time (including time for NaCl flush), total volume infused, and, if necessary, any infusion interruption with explanation will be documented and entered into the subject's source documentation records and eCRF.

6.1.3 Treatment Period 2 for Each Cohort

Subjects will receive Alpha-1 15%, administered as weekly SC infusions over 8 weeks in Treatment Period 2. The first 4 weekly SC infusions will be administered under supervision in the clinic. A trained homecare nurse must administer all SC infusions that are administered

away from the study site. The selected pump, specifically designed for SC infusions, will be provided for individual use to each subject prior to Treatment Period 1. The exact Alpha-1 15% dose (and dose volume) administered based on the predetermined conversion factor will be documented and entered into the subject's source documentation records and eCRF.

The planned volumes and rates of SC administration will be dependent upon various factors such as the subject's weight and tolerability. The investigator is to determine the number of SC infusion sites required based on total volume to be delivered and subject comfort. The principal investigator is not to exceed 8 infusion sites per infusion and the minimum distance between infusion sites is recommended to be no less than 2 inches. The target infusion rate will be no greater than 25 mL/hour/site as tolerated by the subject and per investigator's discretion. Subjects are to be observed for a minimum of 60 minutes post-IP administration for safety.

Details regarding infusion rate and infusion administration are located in the pharmacy/study manual. The number of injection sites, infusion rate, and the specific times of the day for the SC infusion may be individualized by the subject and investigator. Subjects may use the same anatomical area or rotate anatomical areas for SC infusions throughout the study. No more than 8 infusion sites per infusion will be used. The minimum distance between infusion sites is recommended to be no less than 2 inches. The target infusion rate will be no greater than 25 mL/hour/site as tolerated by the subject and per the investigator's discretion; the investigator will tailor the infusion configuration for each subject. Once the target infusion rate is achieved, it should not be changed in the middle of an infusion unless the subject experiences tolerability issues at that infusion rate. In the event that the subject is not able to tolerate the set infusion rate, the rate may be decreased for better tolerability.

The total volume prepared, total volume infused, number of infusion sites, infusion site location(s), infusion start date/time, infusion end date/time, the final rate of infusion, and other SC infusion information will be recorded in the subject's source documentation records and entered into the eCRF. In addition, SC infusion site reactions will be recorded.

6.2 Prior and Concomitant Therapy

Concomitant medications must be recorded in the CRF/eCRF, including the trade and generic names of the medication, the dose, the route of administration, and the duration of the medication (frequency).

6.2.1 Prohibited Medications Prior to Study Participation

Use of the following medications, as specified below, would exclude a subject from participating in this study:

- Systemic steroids above a stable dose equivalent to 5 mg/day prednisone (e.g., 10 mg every 2 days) within 4 weeks prior to the Single-Dose Week 1 (Baseline) Visit (Note: inhaled steroids are not considered systemic steroids)
- Systemic or aerosolized antibiotics for a COPD exacerbation within 4 weeks prior to the Single-Dose Week 1 (Baseline) Visit.

6.2.2 Prohibited Concomitant Medications during the Study

Use of the following medications is prohibited during the study participation (includes the Follow-up Period):

- Any Alpha$_1$-PI product other than the IPs for this study
- Investigational products not part of this study

6.2.3 Restricted Concomitant Medications during the Study

Use of systemic steroids above a stable dose equivalent to 5 mg/day prednisone (e.g., 10 mg every 2 days) is not allowed during study participation; however, use of systemic steroids below a stable dose equivalent to 5 mg/day prednisone is permitted. For subjects receiving a permissible stable dose of systemic steroids, it is recommended to maintain the same dose throughout the study.

6.3 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of the IP dose as prepared by the pharmacist, or designee, must be recorded in the subject's source documentation records and eCRF.

7 ASSESSMENT OF SAFETY AND PHARMACOKINETICS

7.1 Primary Safety Variables

- AEs, suspected ADRs (or potentially related AEs), infusions site reactions (to be reported as AEs), SAEs, and AEs and SAEs leading to discontinuation.
- COPD exacerbations
- Vital signs (HR, BP, RR, and T)
- PFTs:
  - FEV_1 [absolute and predicted]
  - FVC
- Clinical laboratory parameters including:
  - Chemistry
  - Hematology
  - Urinalysis
- Immunogenicity assessments

7.2 Pharmacokinetic (PK) Variables

PK variables include the following single-dose PK parameters of Alpha$_1$-PI, following the single dose of Alpha-1 15% at Single-Dose Week 1, measured using both antigenic content and functional activity assays:

- AUC of Alpha$_1$-PI from time 0 (pre-dose) to time of last quantifiable concentration (AUC_{0-t})
- AUC of Alpha$_1$-PI from time 0 (pre-dose) extrapolated to infinite time ($AUC_{0-\infty}$)
- Percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{ex}$)
- AUC of Alpha$_1$-PI from time 0 to 7 days ($AUC_{0-7\ days}$)
- Maximum concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Clearance (CL)
- Terminal half-life ($t_{1/2}$)
- Volume of distribution (V_d)
- Baseline-corrected AUC_{0-t}, $AUC_{0-\infty}$, $\%AUC_{ex}$, $AUC_{0-7\ days}$, C_{max}, CL, $t_{1/2}$, and V_d, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1)

In addition, PK variables include the following steady-state PK parameters of Alpha$_1$-PI, following the last repeat dose of Alpha-1 15% at Repeat-Dose Week 8, measured using both antigenic content and functional activity assays:

- Steady-state AUC of Alpha$_1$-PI over the weekly dosing interval (from 0 to 7 days) ($AUC_{0-7\ days}$)
- Steady-state mean trough Alpha$_1$-PI level, calculated as the average value of the trough measurements obtained at Repeat-Dose Weeks 6, 7, 8, and 9.
- C_{max}
- t_{max}
- CL
- $t_{1/2}$
- V_d
- Accumulation ratio, calculated as $AUC_{0-7\ days}$ following repeat-dose divided by $AUC_{0-7\ days}$ following single-dose.
- Time-invariance ratio, calculated as $AUC_{0-7\ days}$ following repeat-dose divided by $AUC_{0-\infty}$ following single-dose.
- Baseline-corrected $AUC_{0-7\ days}$, mean trough, C_{max}, CL, $t_{1/2}$, V_d, accumulation ratio, and time-invariance ratio, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1)

NOTE: If the dosing interval (τ) for the repeat-dose SC regimen is different from weekly (i.e., 7 days), the calculation of mean trough above will be adjusted to use appropriate trough samples only, and $AUC_{0-\tau}$ will be calculated in place of $AUC_{0-7\ days}$.

7.3 Exploratory Variable

Subject satisfaction with SC treatment via a written questionnaire following Treatment Period 2.

Additional exploratory PK endpoints include the following steady-state PK parameters of Alpha$_1$-PI, following the 8th weekly IV infusion of Liquid Alpha$_1$-PI at Intravenous Week 8, measured using both antigenic content and functional activity assays:

- Steady-state AUC of Alpha$_1$-PI over the weekly dosing interval (from 0 to 7 days) ($AUC_{0\text{-}7\ days}$)
- Steady-state mean trough Alpha$_1$-PI level, calculated as the average value of the trough measurements obtained at Intravenous Weeks 8 and 9.
- C_{max}
- t_{max}
- CL
- $t_{1/2}$
- V_d
- Baseline-corrected $AUC_{0\text{-}7\ days}$, mean trough, C_{max}, CL, $t_{1/2}$, V_d, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1)

7.4 Methods and Timing for Assessing, Recording, and Analyzing Safety and Pharmacokinetics Parameters

7.4.1 Observations and Measurements

The following is a description of the procedures/assessments to take place at each study visit. See the Schedule of Study Procedures and Events in Appendix 1. Weekly visits occurring after the Single-Dose Week 1 (Baseline) Visit should be scheduled at the protocol-specified week relative to the date of the Week 1 Visit of each period; a +1-day window is allowed for the weekly visits. Unscheduled visits may be conducted if deemed necessary for the purpose of subject safety.

7.4.1.1 Assessment Periods

This study consists of two cohorts and each cohort will consist of an up to 30-day Screening Phase, a 7-day Treatment Period 1, a 21-day Washout / Serial PK Phase, an up to 18 months of a Single-Dose Data Evaluation Phase, a 56-day Treatment Period 2, and 7-day off-treatment Follow-up Phase.

7.4.1.2 Screening Phase

All prospective subjects will start their participation in the study upon the signing of the informed consent form (ICF) prior to the collection of any screening assessments or the conduct of any study procedures. Subjects will be assessed for study eligibility for up to 30 days (i.e., 4 weeks) during the Screening Period. The maximum duration for the Screening Period, 30 days, is to allow sufficient time for reporting of genotyping and phenotyping results for potential subjects whose AATD genotype has not been previously documented (see Inclusion Criterion 2) as well as a washout of prior augmentation therapy. Subjects receiving Alpha$_1$-PI augmentation therapy of any kind MUST STOP their ongoing

augmentation therapy during the Screening Period to allow for a washout period prior to receiving Alpha-1 15% in Treatment Period 1. **A minimum washout period of 25 days is required between the last dose of the pre-study augmentation therapy and the first Alpha-1 15% single dose at Single-Dose Week 1**. Subjects who initially fail to meet eligibility criteria during the Screening Period may be re-screened once upon consultation with the Sponsor. Subjects who fail to meet eligibility criteria upon re-screen are screen failures and will not be eligible to participate in the study.

SCREENING PERIOD (UP TO 30 DAYS PRIOR TO SINGLE-DOSE WEEK 1 [BASELINE] VISIT):

Subjects will be screened for enrollment in this study. The following procedures and assessments will be performed during the Screening Visit:

- Obtain informed consent
- Assess inclusion and exclusion criteria to determine subject eligibility
- Assign subject number
- Collect medical history and demography *(age [year of birth], age at screening [years], gender [if female, fertility status], race, and ethnicity)*
- Assess AEs, concomitant medication, and COPD exacerbations
- Perform physical examination (excludes breast and genitourinary examination)
- Record height
- Record weight
- Obtain pre- and post-bronchodilator PFTs (FEV_1 [absolute and predicted] and FVC)
- Collect blood and urine samples for laboratory tests
  - clinical laboratory assessments (clinical chemistry, hematology, urinalysis)
  - blood for genotyping (i.e., allelic discrimination) and phenotyping for AATD, to be performed only if the genotype has not yet been documented; Note: The laboratory tests will not detect "at-risk" alleles and prior documentation must exist in the subject's medical records.
  - blood for HAV, HBV, HCV, HIV, and B19V virus safety (viral NAT and viral serology) retain samples
  - blood for $Alpha_1$-PI level, to be performed only if the total $Alpha_1$-PI level <11 µM has not yet been documented
  - urine pregnancy test (potential child-bearing females only)
  - urine cotinine
  - Washout of prior augmentation therapy; Subject to be instructed to STOP their ongoing Alpha1-PI augmentation therapy during the Screening Period to allow for a washout period prior to receiving Alpha-1 15% in Treatment Period 1.

7.4.1.3 Treatment Phase

Eligible subjects will enter the Treatment Phase and will receive Alpha-1 15% subcutaneously within each treatment period. During the Single-Dose Data Evaluation period, subjects will receive Liquid Alpha1-PI intravenously. Enrollment will occur in

2 sequential cohorts of approximately 8 subjects each. **Subjects cannot enroll into both cohorts**.

The first Cohort will include approximately 8 subjects receiving the 72 mg/kg (Cohort 1) starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose), safety data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (60 mg/kg for Cohort 1) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) for all subjects will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 1. Following completion of Treatment Period 2 (Repeat-Dose) for subjects in Cohort 1, the iSRC will evaluate safety data prior to initiating Cohort 2 (180 mg/kg). Dosing must not commence to Cohort 2 until Grifols has provided written confirmation to the PI. If the iSRC determines it is safe to proceed with dose escalation, Cohort 2 will be initiated.

The second cohort will include approximately 8 subjects receiving the 180 mg/kg (Cohort 2) dose of Alpha-1 15% starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). Furthermore, enrollment into Cohort 2 will only commence once the iSRC has reviewed safety data from the entire cohort of subjects treated with 72 mg/kg. To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose) phase, safety data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (120 mg/kg for Cohort 2) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) from a subset of subjects will be evaluated by the study team to determine/confirm the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 2.

Furthermore, within each cohort dosing will be staggered subject by subject for the first 4 subjects with a 7-day waiting period in between each subject, to allow assessment of the safety and tolerability by the iSRC. If the iSRC determines it is appropriate and safe, the last 4 subjects within the cohort can be enrolled without the staggered approach.

7.4.1.3.1 TREATMENT PERIOD 1 (SINGLE-DOSE)

SINGLE-DOSE WEEK1 (BASELINE) VISIT/SD-SC#1 (TO TAKE PLACE AT STUDY SITE ONLY):

The Single-Dose Week 1 (Baseline) Visit must be performed at the study site. The Single-Dose Week 1 (Baseline) Visit will be conducted after all screening laboratory results

are available and all inclusion (and no exclusion) criteria have been satisfied. Eligible subjects will return to the study site for the Single-Dose Week 1 (Baseline) Visit within 30 days following the Screening Visit. The Single-Dose Week 1 (Baseline) initiates Treatment Period 1 comprising of a single-dose administered subcutaneously.

The following procedures and assessments will be performed during the Single-Dose Week 1 (Baseline) Visit prior to infusion:

- Review inclusion and exclusion criteria to confirm subject eligibility
- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of SC infusion
- Record weight (the subjects recorded weight will be used by the pharmacist, or designee, to calculate the IP infusion dose for this study visit) prior to initiation of SC infusion
- Collect blood and urine samples for laboratory tests:
  - blood for virus safety retain samples
  - blood for immunogenicity testing
  - blood PK serial sample for $Alpha_1$-PI concentration within 25 minutes prior to initiation of infusion
  - urine pregnancy test (potential child-bearing females only)
  - retains for possible future biomarker analysis (optional)

The following procedures and assessments will be performed during the Single-Dose Week 1 (Baseline) Visit at the time of infusion:

- Administer Alpha-1 15% by SC infusion by qualified study site personnel and record SC infusion information
- Record vital signs (HR, BP, RR, and T) 30 minutes (± 5 minutes) after initiation of the infusion
- Assess local infusion site reactions (to be reported as AEs)

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of the infusion
- Observe for safety signs/symptoms for at least 60 minutes after completion of the infusion
- Collect PK serial blood sample for $Alpha_1$-PI concentration at the following time points after completion of infusion:
  - Within 5 minutes following completion time
  - 1 hour (± 15 minutes)
  - 4 hours (± 30 minutes)
  - 8 hours (± 2 hours)*
  - 1 day (24 ± 4 hours)*
  - 2 days (48 ± 4 hours)*
  - 3 days (72 ± 4 hours)*
  - 4 days (96 ± 4 hours)*
  - 5 days (120 ± 4 hours)*

– 6 days (144 ± 4 hours)*
– 7 days (+ 1 day)†

*NOTE: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, 3, 4, 5, and 6 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

†NOTE: The PK serial sample taken at 7 days following completion of the Single-Dose Week 1 infusion will be drawn at the Single-Dose Week 2 Visit.

7.4.1.3.2 WASHOUT/SERIAL PK

SINGLE-DOSE WEEK 2/WASHOUT 1/SERIAL PK (TO TAKE PLACE AT STUDY SITE ONLY):

Single-Dose Week 2 must be performed at the study site. No IP or any other Alpha$_1$-PI augmentation therapy is to be administered during the Washout/Serial PK period. Site personnel will remind the subject to continue to remain off all Alpha$_1$-PI augmentation therapy. The Single-Dose Week 2 (Washout 1/Serial PK) initiates the washout/serial PK time between Treatment Period 1 (single-dose) and Treatment Period 2 (repeat-dose).

The following procedures will be performed:

- Assess AEs, local infusion site reactions, concomitant medication, and COPD exacerbations
- Collect blood samples for laboratory tests:
  - blood for Alpha$_1$-PI concentration 7 days (+1 day) following completion time of the Single-Dose Week 1 infusion

SINGLE-DOSE WEEKS 3 AND 4 WASHOUT 2 AND 3 /SERIAL PK (STUDY SITE OR ALTERNATIVE SITE):

Single-Dose Weeks 3 and 4 Visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. No IP or any other Alpha$_1$-PI augmentation therapy is to be administered during the Washout/Serial PK period. Site or trained healthcare personnel will remind the subject to continue to remain off all Alpha$_1$-PI augmentation therapy.

The following procedures and assessments will be performed during the visits:

- Assess AEs, local infusion site reactions, concomitant medication, and COPD exacerbations
- Collect blood samples for laboratory tests:
  - blood for Alpha$_1$-PI concentration 14 (+1 day) and 21 (+1 day) days following completion time of the Single-Dose Week 1 infusion

7.4.1.3.3 SINGLE-DOSE DATA EVALUATION PERIOD (WEEKLY IV INFUSIONS)

SINGLE-DOSE WEEK 5/INTRAVENOUS WEEK 1 (STUDY SITE ONLY):

The Single-Dose Week 5/Intravenous Week 1 Visit must be performed at the study site.

The following procedures and assessments will be performed during the Single-Dose Week 5/Intravenous Week 1Visit prior to the IV#1 infusion:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of intravenous infusion
- Record weight (the subjects recorded weight will be used by the pharmacist, or designee, to calculate the IP infusion dose for this study visit)
- Collect blood and urine samples for laboratory tests:
  - blood for virus safety retain samples
  - urine pregnancy test (potential child-bearing females only)
  - obtain pre- and post-bronchodilator PFTs (FEV_1 [absolute and predicted] and FVC)
  - clinical laboratory assessments (clinical chemistry, hematology, urinalysis)
  - blood for $alpha_1$-PI concentration 28 (+1 day) days following completion time of the Single-Dose Week 1 infusion
  - immunogenicity testing

The following procedures and assessments will be performed during the Single-Dose Week 5/Intravenous Week 1 Visit at the time of infusion:

- Administer Liquid $Alpha_1$-PI by IV infusion
- Record vital signs (HR, BP, RR, and T) within 10 minutes after initiation of the infusion

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of infusion (after NaCl flush)
- Observe for safety signs/symptoms for at least 30 minutes after completion of the infusion

INTRAVENOUS WEEK 2 UP TO WEEK 7 AND INTRAVENOUS WEEK 10 UP TO WEEK 78 (STUDY SITE OR ALTERNATIVE SITE):

The following procedures and assessments will be performed from Intravenous Week 2 up to Week 7 and from Intravenous Week 10 up to Week 78 Visits:

Visits at Intravenous Week 2 up to Week 7 and from Intravenous Week 10 up to Week 78 may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

The following procedures and assessments will be performed prior to infusion at Intravenous Week 2 up to Week 7 and from Intravenous Week 10 up to Week 78 Visits:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of infusion

The following procedures and assessments will be performed at the time of infusion during visits at Intravenous Week 2 up to Week 7 and from Intravenous Week 10 up to Week 78 Visits:

- Administer Liquid $Alpha_1$-PI by IV infusion
- Record vital signs (HR, BP, RR, and T) within 10 minutes after initiation of the infusion

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of infusion (after NaCl flush)
- Observe for safety signs/symptoms for at least 30 minutes after completion of the infusion

INTRAVENOUS WEEK 8 /IV#8 (STUDY SITE ONLY)

The Intravenous Week 8 Visit must be performed at the study site. The following procedures and assessments will be performed prior to infusion at the Intravenous Week 8 Visit:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of infusion
- Collect PK serial blood sample for $Alpha_1$-PI concentration within 25 minutes prior to initiation of infusion (Note: this sample also serves as the trough $Alpha_1$-PI measurement at Intravenous Week 8)

The following procedures and assessments will be performed at the time of infusion during the Intravenous Week 8 visit:

- Administer Liquid Alpha 1 by IV infusion
- Record vital signs (HR, BP, RR, and T) within 10 minutes after initiation of the infusion
- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of infusion (after NaCl flush)

The following procedures and assessments will be performed after infusion during the Intravenous Week 8 visit:

- Collect PK serial blood sample for $Alpha_1$-PI concentration at the following time points after completion of infusion:
  - Within 5 minutes following completion time (after NaCl flush)
  - 15 minutes (± 5 minutes)
  - 30 minutes (± 5 minutes)
  - 1 hour (± 10 minutes)
  - 2 hours (± 15 minutes)
  - 4 hours (± 30 minutes)

- 8 hours (± 2 hours)*
- 1 day (24 ± 4 hours)*
- 2 days (48 ± 4 hours)*
- 5 days (120 ± 4 hours)*
- 7 days (+ 1 day)†

*NOTE: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, and 5 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

†NOTE: The PK serial sample taken at 7 days following completion of the Intravenous Week 8 infusion will be drawn at the Intravenous Week 9 Visit prior to the Intravenous Week 9 infusion. This sample also serves as the trough Alpha$_1$-PI measurement at Intravenous Week.

INTRAVENOUS WEEK 9 /IV#9 (STUDY SITE ONLY)

NOTE: All subjects will have a minimum of 9 weeks of Liquid Alpha$_1$-PI before proceeding to repeat-dose SC period (Treatment Period 2).

The Intravenous Week 9 Visit must be performed at the study site. The following procedures and assessments will be performed prior to infusion at the Intravenous Week 9 Visit:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of infusion
- Collect PK serial blood sample for Alpha$_1$-PI concentration 7 days (+ 1 day) following completion time of the Intravenous Week 8 infusion (Note: this sample also serves as the trough Alpha$_1$-PI measurement at Intravenous Week 9)

The following procedures and assessments will be performed at the time of infusion during the Intravenous Week 9 visit:

- Administer Liquid Alpha 1 by IV infusion
- Record vital signs (HR, BP, RR, and T) within 10 minutes after initiation of the infusion
- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of infusion (after NaCl flush)

7.4.1.3.4 TREATMENT PERIOD 2 (REPEAT-DOSE)

NOTE: The trough and serial PK sampling schedules in Treatment Period 2 (Repeat-Dose) described below correspond to a weekly (i.e., 7 days) dosing interval (τ). Repeat-dose SC regimens in Treatment Period 2 will be determined after reviewing single-dose safety and PK data from Treatment Period 1. If the dosing interval (τ) for the repeat-dose SC regimen is different from weekly (i.e., 7 days), the trough and serial PK sampling schedules in Treatment Period 2 will be adjusted to allow for a full characterization of the mean trough and $AUC_{0-\tau}$.

REPEAT-DOSE WEEK 1/RD-SC#1 (STUDY SITE ONLY):

The Repeat-Dose Week 1 Visit must be performed at the study site. The Repeat-Dose Week 1 initiates Treatment Period 2 comprising of repeat dosing. This visit should be performed 7 days after the last Intravenous Week Visit (+ 1-day window).

The following procedures and assessments will be performed during the Repeat-Dose Week 1 Visit prior to infusion:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of SC infusion
- Record weight (the subjects recorded weight will be used by the pharmacist, or designee, to calculate the IP infusion dose for this study visit and subsequent weekly infusions) prior to initiation of SC infusion
- Obtain pre- and post-bronchodilator PFTs (FEV_1 [absolute and predicted] and FVC)
- Collect blood and urine samples for laboratory tests:
  - clinical laboratory assessments (clinical chemistry, hematology, urinalysis)
  - blood for virus safety retain samples
  - blood for immunogenicity testing
  - urine pregnancy test (potential child-bearing females only)
  - retains for possible future biomarker analysis (optional)

The following procedures and assessments will be performed during the Repeat-Dose Week 1 Visit at the time of infusion:

- Administer Alpha-1 15% by SC infusion by qualified study site personnel and record SC infusion information
- Record vital signs (HR, BP, RR, and T) 30 minutes (± 5 minutes) after initiation of the infusion
- Assess local infusion site reactions (to be reported as AEs)

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of the infusion
- Observe for safety signs/symptoms for at least 60 minutes after completion of the infusion

REPEAT-DOSE WEEKS 2, 3, AND 4/RD-SC#2, RD-SC#3, AND RD-SC#4 (STUDY SITE ONLY):

Repeat-Dose Weeks 2, 3, and 4 Visits must be performed at the study site. The following procedures will be performed prior to infusion:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of infusion
- *Repeat-Dose Week 4 Visit only:*

- Collect blood sample for pre-infusion (trough) Alpha$_1$-PI concentration (collect but test only if deemed appropriate [e.g., unexpected PK profile])
- Collect blood for virus safety retain samples
- Collection of blood for immunogenicity testing (collect but test only if deemed appropriate [e.g., unexpected PK profile])
- Obtain pre- and post-bronchodilator PFTs (FEV_1 [absolute and predicted] and FVC)

The following procedures and assessments will be performed at the time of infusion during the visit:

- Administer Alpha-1 15% by SC infusion by qualified study site personnel and record SC infusion information
- Record vital signs (HR, BP, RR, and T) 30 minutes (± 5 minutes) after initiation of the infusion
- Assess local infusion site reactions (to be reported as AEs)

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of the infusion
- Observe for safety signs/symptoms for at least 60 minutes after completion of the infusion

REPEAT-DOSE WEEKS 5, 6, AND 7 / RD-SC#5, RD-SC#6, AND RD-SC#7 (STUDY SITE OR ALTERNATIVE SITE):

Repeat-Dose Weeks 5, 6, and 7 may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

The following procedures will be performed prior to infusion:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of infusion
- *Repeat-Dose Weeks 6 and 7 Visits only:*
  - Collect blood sample for pre-infusion Alpha$_1$-PI concentration
- *Repeat-Dose Week 7 Visit only:*
  - Collect blood sample for virus safety retain samples

The following procedures and assessments will be performed at the time of infusion:

- Administer Alpha-1 15% by SC infusion by qualified study site personnel and record SC infusion information
  - If the visit is performed an at alternate site, a trained homecare nurse must administer all SC infusions that are administered away from the study site.
- Record vital signs (HR, BP, RR, and T) 30 minutes (± 5 minutes) after initiation of the infusion
- Assess local infusion site reactions (to be reported as AEs)

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of the infusion
- Observe for safety signs/symptoms for at least 60 minutes after completion of the infusion

REPEAT-DOSE WEEK 8 / RD-SC#8 (STUDY SITE ONLY):

The Repeat-Dose Week 8 Visit must be performed at the study site. The last repeat dose of IP for the study will be administered during the Repeat-Dose Week 8 Visit. The following procedures and assessments will be performed prior to infusion:

- Assess AEs, concomitant medication, and COPD exacerbations
- Record vital signs (HR, BP, RR, and T) within 30 minutes prior to initiation of infusion
- Collect PK serial blood sample for $Alpha_1$-PI concentration within 25 minutes prior to initiation of infusion (Note: this sample also serves as the trough $Alpha_1$-PI measurement at Repeat-Dose Week 8)

The following procedures and assessments will be performed at the time of infusion:

- Administer Alpha-1 15% by SC infusion by qualified study site personnel and record SC infusion information
- Record vital signs (HR, BP, RR, and T) 30 minutes (± 5 minutes) after initiation of the infusion
- Assess local infusion site reactions (to be reported as AEs)
- Observe for safety signs/symptoms for at least 60 minutes after completion of the infusion

The following procedures and assessments will be performed after infusion:

- Record vital signs (HR, BP, RR, and T) within 30 minutes after completion of the infusion
- Observe for safety signs/symptoms for at least 60 minutes after completion of the infusion
- Collect PK serial blood sample for $Alpha_1$-PI concentration at the following time points after completion of infusion:
  - Within 5 minutes following completion time
  - 1 hour (± 15 minutes)
  - 4 hours (± 30 minutes)
  - 8 hours (± 2 hours)*
  - 1 day (24 ± 4 hours)*
  - 2 days (48 ± 4 hours)*
  - 3 days (72 ± 4 hours)*
  - 4 days (96 ± 4 hours)*
  - 5 days (120 ± 4 hours)*
  - 6 days (144 ± 4 hours)*
  - 7 days (+ 1 day)†

*NOTE: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, 3, 4, 5, and 6 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

†NOTE: The PK serial sample taken at 7 days following completion of the Repeat-Dose Week 8 infusion will be drawn at the Repeat-Dose Week 9 Visit.

7.4.1.4 Follow-up Phase

REPEAT-DOSE WEEK 9 (FINAL VISIT) / EARLY WITHDRAWAL VISIT (STUDY SITE ONLY):

The Repeat-Dose Week 9 (Final Visit) will be scheduled 1 week after the last repeat SC infusion of IP at Repeat-Dose Week 8 and must be performed at the study site. If a subject discontinues the study after the single dose at Single-Dose Week 1 and prior to starting Single-Dose Data Evaluation (weekly IV infusions), the subject will be requested to return to the study site as close as possible to 4 weeks (28 days) after the single SC infusion of IP to have the below procedures and assessments conducted. If a subject discontinues the study after starting Single-Dose Data Evaluation (weekly IV infusions), the subject will be requested to return to the study site as close as possible to 1 week (7 days) after the last repeat IV or SC infusion of IP to have the below procedures and assessments conducted.

The following procedures and assessments will be performed during the visit:

- Assess AEs, local infusion site reactions, concomitant medication, and COPD exacerbations
- Perform physical examination (excludes breast and genitourinary examination)
- Record vital signs (T, RR, HR, BP)
- Obtain pre-and post-bronchodilator PFTs (FEV_1 [absolute and predicted] and FVC)
- Collect blood and urine samples for laboratory tests:
  - clinical laboratory assessments (clinical chemistry, hematology, urinalysis)
  - blood for virus safety retain samples
  - urine pregnancy test (potential child-bearing females only)
  - urine cotinine
  - blood for immunogenicity testing
  - retains for possible future biomarker analysis (optional)
- Administer subject satisfaction with SC treatment questionnaire
- *Final Visit only:*
  - PK serial blood sample for Alpha$_1$-PI concentration 7 days (+1 day) following completion time of the Repeat-Dose Week 8 infusion
- *Early Withdrawal Visit only:*
  - blood for Alpha$_1$-PI concentration

7.4.2 Description of Laboratory Tests and Procedures

Detailed descriptions of laboratory test procedures are located in the study Laboratory Manual. Table 7-1 provides an example summary of the laboratory tests conducted for this study.

Table 7-1 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel	Description	Location
Hematology[a]	Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, WBC with differential; ARC	Central
Chemistry[a]	Sodium, potassium, creatinine, calcium, BUN, bicarbonate, albumin, AST, ALT, ALP, glucose, total protein, total bilirubin	Central
Genotyping/phenotyping[a]	For diagnosis of AATD (if needed)	Specialty
Virus safety retain samples[a, c]	Screening, Single-Dose Weeks 1[b] and 5[b]/Intravenous Week 1[b]; Repeat-Dose Weeks 1[b], 4[b], 7[b], 9[b] (Final/Early Withdrawal): Collect retain samples for HAV RNA, HBV DNA, HCV RNA, HIV RNA, B19V DNA testing, as well as HAV antibody differential (IgM/ IgG), HBV core antibody differential (IgM/IgG), HB surface antigen (HBsAg), HCV antibody, HIV-1/-2 + Group O antibody testing, and B19V antibody differential (IgM/IgG) testing	Central
Alpha$_1$-PI Concentration [c]	Samples at Single-Dose Weeks 1 to 5/Intravenous Week 1; Intravenous Weeks 8 to 9; Repeat-Dose Weeks 6, 7, 8 to 9 (Final): Alpha$_1$-PI concentration for diagnosis of AATD (if needed) and PK analysis (as measured by both antigenic content and functional activity [potency] assays) Samples at Repeat-Dose Week 4 and Early Withdrawal Visit will be collected for retentions.	Specialty
Alpha$_1$-PI Immunogenicity [c, d]	Samples at Single-Dose Weeks 1 and 5/Intravenous Week 1; Repeat-Dose Weeks 1, 4, and 9 (Final/Early Withdrawal Visit): Antibodies to Alpha$_1$-PI; neutralizing antibody for samples that test positive for Alpha$_1$-PI antibodies Samples at Repeat-Dose Week 4 will be collected for retentions.	Specialty
Urinalysis[a]	Microscopic evaluation is done only with cause. pH, protein, glucose, and blood	Central
Urine cotinine[a]	Cotinine level	Central
Urine pregnancy test[a]	Dipstick urine pregnancy test for females of child-bearing potential	Local
Blood for biomarkers[e]	Plasma and cellular pellet samples to be frozen and retained up to 5 years after the end of the study for possible future analysis	Central

Abbreviations: AATD = alpha$_1$-antitrypsin deficiency; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARC = absolute reticulocyte count; AST = aspartate aminotransferase; B19V = parvovirus B19; BUN = blood urea nitrogen; DNA = deoxy ribonucleic acid, HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; RNA = ribonucleic acid WBC = white blood cell.

[a] Samples collected for laboratory analyses that are non-analyzable due to any factor (i.e., lost, quantity not sufficient, laboratory error) need to be recollected by contacting the subject and rearranging for re-sampling.

[b] Virus safety (viral nucleic acid testing [NAT] and viral serology) samples will be collected prior to the administration of IP.

[c] Samples will be retained until all analyses in support of the study are complete.

[d] If a subject has a positive anti-drug antibody (ADA) response that would require follow-up testing to determine if the result is a transient or sustained response, additional blood samples may be collected for a time period of up to 1 year following the positive ADA response. Furthermore, aliquots of immunogenicity samples will be retained for up to 5 years post-study for possible future analysis. Sample must be collected prior to administration of IP.

[e] Biomarker sample collection is optional (subject may opt out). If a subject opts out of this collection, samples will not be collected, processed, or shipped for storage. Samples will be collected prior to the administration of IP at Single-Dose Week 1 (Baseline) Single-Dose Week 5/Intravenous Week 1, Repeat Dose 1 and Repeat Dose Week 9.

7.4.2.1 Virus Safety Testing

Blood samples for HAV, HBV, HCV, HIV, and B19V virus safety (viral nucleic acid testing [NAT] and viral serology) testing will be collected at the Screening visit, Single-Dose Week 1 (Baseline), Single-Dose Week 5/Intravenous Week 1, Repeat-Dose Weeks 1, 4, and 7 prior to IP administration, and at the Repeat-Dose Week 9 (Final/Early Withdrawal Visit) and tested only if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or B19V infection while participating in the study.

Viral NAT and viral serology samples will be frozen and retained for up to 5 years following completion of the study in the event that additional testing is required in the future for purposes of this study only (i.e., repeat testing or repeat safety testing). If samples collected for laboratory analyses are non-analyzable due to various factors (i.e., lost, quantity not sufficient/useful, laboratory error), they will need to be recollected by contacting the subject and arranging for re-sampling. Additional blood samples for viral NAT and viral serology testing may be collected and tested during the study only if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or B19V infection while participating in the study.

7.4.2.2 Immunogenicity

Blood samples for immunogenicity testing will be drawn prior to IP administration at the Single-Dose Weeks 1 and 5/Intravenous Week 1, Repeat-Dose Weeks 1, 4, and 9 (Final/Early Withdrawal Visit). Samples collected at Single-Dose Weeks 1 and 5/Intravenous Week 1 and Repeat-Dose Weeks 1 and 9 (Final/Early Withdrawal Visit) will be tested for immunogenicity; the samples collected at Repeat-Dose Week 4 will be tested for immunogenicity only if deemed appropriate (e.g., unexpected PK profile).

Any samples that test positive for Alpha$_1$-PI antibodies will be tested for neutralizing antibodies and antibody titer. Immunogenicity testing will be performed using validated assays in a multi-tiered approach. Additionally, if a subject has a positive anti-drug antibody (ADA) response that would require follow-up testing to determine if the result is a transient or sustained response, additional blood samples may be collected for a time period of up to 1 year following the positive ADA response. The clinical trial informed consent will include

language to accommodate for additional blood sampling if necessary due to a positive ADA response. Furthermore, aliquots of immunogenicity samples will be retained for up to 5 years post study for possible future analysis of immunogenicity.

Blood samples for Alpha$_1$-PI concentration will be drawn pre-infusion at the same time points as the immunogenicity samples. Alpha$_1$-PI samples that are not part of the PK measurements (i.e., Repeat-Dose Week 4 [see Section 7.4.3]), will be collected, but not tested unless a subject has a positive ADA response that requires follow-up testing to determine if the result is a transient or sustained response.

7.4.2.3 Urine Cotinine

In the Screening Period, any subject with a positive urine cotinine due to smoking will be ineligible for study participation.

7.4.3 Drug Concentration Measurements

The concentration of Alpha$_1$-PI will be measured in trough (pre-infusion) and serial blood samples from all subjects in Treatment Period 1 (i.e., at Single-Dose Weeks 1 to 5), during the Single-Dose Data Evaluation Period (i.e., at Intravenous Weeks 8 to 9) and at the end of Treatment Period 2 (i.e., at Repeat-Dose Weeks 6, 7, and 8 to 9) for the purpose of PK analysis. Thus, each subject will have Alpha$_1$-PI concentration blood samples drawn for PK analysis for Alpha-1 15% (72 and 180 mg/kg) and Liquid Alpha$_1$-PI (60 and 120 mg/kg). Alpha$_1$-PI concentrations for trough and serial blood samples will be measured by both antigenic content and functional activity (potency) assays; assays will be validated according to current regulatory guidelines and industry expectations. Alpha$_1$-PI concentrations as measured by antigenic content assay will be used for the purpose of evaluating non-inferiority for the primary objective of this study (see Section 3.1.1).

7.4.3.1 Treatment Period 1

A total of 15 serial PK blood samples will be collected in Treatment Period 1 at the time of the Single-Dose Week 1 IP infusion as follows:

- Within 25 minutes prior to infusion
- Within 5 minutes after SC infusion completion time
- 1 hour (± 15 minutes)
- 4 hours (± 30 minutes)
- 8 hours (± 2 hours)*
- 1 day (24 ± 4 hours)*
- 2 days (48 ± 4 hours)*
- 3 days (72 ± 4 hours)*
- 4 days (96 ± 4 hours)*
- 5 days (120 ± 4 hours)*
- 6 days (144 ± 4 hours)*
- 7 days (+ 1 day)†

- 14 days (+ 1 day)†
- 21 days (+ 1 day)†
- 28 days (+ 1 day)^

*NOTE: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, 3, 4, 5, and 6 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

†NOTE: The PK serial sample taken at 7, 14, and 21 days following completion of the Single-Dose Week 1 infusion will be drawn at the Single-Dose Weeks 2, 3, and 4, respectively.

^NOTE: A blood sample will be collected for endogenous Alpha$_1$-PI concentration 28 days following completion of the Single-Dose Week 1 infusion (Note: sample is considered the last serial PK sample following single-dose. In addition, it will be used to calculate the baseline-corrected PK parameters of Alpha$_1$-PI for both single-dose and repeat-dose SC administrations as well as for repeat-dose IV administration). This sample will be taken at the Single-Dose Week 5/Intravenous Week 1 visit prior to the IV#1 infusion.

7.4.3.2 Single-Dose Data Evaluation Period (Liquid Alpha$_1$-PI)

A total of 12 serial PK blood samples will be collected during the Single-Dose Data Evaluation Period at the time of the Intravenous Week 8 IP infusion as follows:

- Within 25 minutes prior to infusion
- Within 5 minutes after infusion completion (after NaCl flush)
- 15 minutes (± 5 minutes) after infusion completion
- 30 minutes (± 5 minutes) after infusion completion
- 1 hour (± 10 minutes) after infusion completion
- 2 hours (± 15 minutes) after infusion completion
- 4 hours (± 30 minutes) after infusion completion
- 8 hours (± 2 hours) after infusion completion
- 1 day (24 ± 4 hours) after infusion completion
- 2 days (48 ± 4 hours) after infusion completion
- 5 days (120 ± 4 hours) after infusion completion, and
- 7 days (+ 1 day) after infusion completion (Note: sample will be drawn at the Intravenous Week 9 Visit prior to the IV#9 IP infusion).

*NOTE: To facilitate the collection of serial PK blood samples, samples for Alpha1-PI concentration taken at 8 hours and 1, 2, and 5 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

7.4.3.3 Treatment Period 2

NOTE: The following serial PK sampling schedule is intended for weekly dosing. If the dosing frequency of the repeat dose regimen is different from weekly after the review of the single-dose PK and safety data, the serial PK sampling schedule will be adjusted to cover the entire steady-state dosing interval.

Additionally, a total of 12 serial PK blood samples will be collected at the end of Treatment Period 2 at the time of the Repeat-Dose Week 8 IP infusion as follows:

- Within 25 minutes prior to infusion
- Within 5 minutes following completion
- 1 hour (± 15 minutes)
- 4 hours (± 30 minutes)
- 8 hours (± 2 hours)*
- 1 day (24 ± 4 hours)*
- 2 days (48 ± 4 hours)*
- 3 days (72 ± 4 hours)*
- 4 days (96 ± 4 hours)*
- 5 days (120 ± 4 hours)*
- 6 days (144 ± 4 hours)*
- 7 days (+1 day)†

  *NOTE: To facilitate the collection of serial PK blood samples, samples for $Alpha_1$-PI concentration taken at 8 hours and 1, 2, 3, 4, 5, and 6 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

  †NOTE: The PK serial sample taken at 7 days following completion of the Repeat-Dose Week 8 infusion will be drawn at the Repeat-Dose Week 9 Visit (Final Visit).

The pre-infusion serial PK sample at Repeat-Dose Week 8 will also as the trough $Alpha_1$-PI measurement at Repeat-Dose Week 8.

8 ASSESSMENT OF SAFETY

8.1 Safety Parameters

Safety of Alpha-1 15% will be evaluated in this study. The following safety endpoints will be assessed in this study:

- AEs, SAEs, and AEs and SAEs leading to discontinuation
- COPD exacerbations
- Vital signs (HR, BP, RR, and T)
- PFTs:
  - FEV_1 [absolute and predicted]

- FVC

- Clinical laboratory parameters including:
  - Chemistry
  - Hematology
  - Urinalysis
- Immunogenicity assessments

8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

8.2.1 Chronic Obstructive Pulmonary Disease Exacerbations

All COPD exacerbations occurring during the study will be recorded. The subject will be assessed for signs and symptoms of exacerbations at each study visit. Given that COPD exacerbations are part of the natural history of AATD, COPD exacerbations will not be reported as AEs unless a COPD exacerbation meets the criteria of a SAE (see Section 8.3.7 and Section 8.3.9).

This study will use the definition of exacerbation published in the "Outcomes for COPD pharmacological trials: from lung function to biomarkers," a report from an American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force (Cazzola, 2008). The definition of an exacerbation of COPD is an increase in respiratory symptoms (dyspnea, increased cough, and/or production of sputum) over baseline that usually requires medical intervention. Exacerbation severity is defined as:

- **Mild:** which involves an increase in one or more respiratory symptoms (dyspnea, cough, and/or sputum) that is controlled by the subject with an increase in the usual medication
- **Moderate:** which requires treatment with systemic steroids and/or antibiotics
- **Severe:** which describes exacerbations that require hospitalization (an emergency department stay >24 hours is considered a hospitalization*)

*Note: Hospitalization is to be considered only hospital admission (including emergency room stay) for equal to or more than 24 hours.

8.2.2 Pulmonary Function Tests

Pulmonary function tests (i.e., spirometry), including FEV_1 (absolute and predicted) and FVC, will be performed according to ATS/ERS guidelines (Miller, 2005) at Screening and Single-Dose Week 5/Intravenous Week 1, and Repeat-Dose Weeks 1, 4, and 9. At each visit in which PFTs are scheduled, testing will be performed both pre- and post-bronchodilator administration. The post-bronchodilator PFT should be performed 15 to 30 minutes after bronchodilator administration. For each PFT, a short-acting bronchodilator (e.g., albuterol) should be administered. It is recommended that the same bronchodilator be used throughout the study.

8.2.3 Immunogenicity Assessments

Single-Dose Weeks 1 and 5/Intravenous Week 1, Repeat-Dose Weeks 1, 4, and 9 (Final/Early Withdrawal Visit). Samples collected at Single-Dose Weeks 1 and 5/Intravenous Week 1 and Repeat-Dose Weeks 1 and 9 (Final/Early Withdrawal Visit) will be tested for immunogenicity; the samples collected at Repeat-Dose Week 4 will be tested for immunogenicity only if deemed appropriate (e.g., unexpected PK profile).

Samples collected prior to exposure and after 8 weeks of exposure to the IP will be sufficient to determine an antibody response based on US Food and Drug Administration immunogenicity guidelines (FDA guidance, 2019; FDA guidance, 2014). Any samples that test positive for Alpha$_1$-PI antibodies will be tested for neutralizing antibodies and antibody titer. Immunogenicity testing will be performed using validated assays in a multi-tiered approach. Additionally, if a subject has a positive ADA response that would require follow-up testing to determine if the result is a transient or sustained response, additional blood samples may be collected for a time period of up to 1 year following the positive ADA response. The clinical trial informed consent includes language to accommodate for additional blood sampling, if necessary, due to a positive ADA response. Furthermore, aliquots of immunogenicity samples will be retained for up to 5 years post-study for possible future analysis of immunogenicity.Adverse Events

Adverse events (including ADRs) occurring at any time between signing of the subject's ICF and the last day of the subject's participation in the clinical trial (i.e., Repeat-Dose Week 9 [Final Visit] or Early Withdrawal Visit) will be reported and recorded in the subject's source documentation records and on the appropriate eCRF entry.

It is the investigator's responsibility to ensure that all AEs are appropriately recorded.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

8.2.5 Clinical Laboratory Evaluations

All clinical laboratory data for renal (sodium, potassium, creatinine, calcium, blood urea nitrogen (BUN), bicarbonate, albumin, glucose), hepatic (ALT, AST, ALP, total protein, and total bilirubin) and hematological parameters (hemoglobin, hematocrit, platelets, red blood cell [RBC] count including RBC morphology, white blood cell [WBC] count with differential) will be listed for each clinical trial subject.

The investigator will be required to classify laboratory results out of the normal range reported by the laboratory as clinically significant or not according to his/her criteria.

Laboratory results out of the normal range judged by the investigator as clinically significant will be considered AEs.

8.2.6 Vital Signs

Vital signs will be measured by a medically certified individual or a nurse according to his/her standard clinical practice. Vital signs will be measured at the following visits:

Single-Dose Weeks 1 (Baseline) and 5/Intravenous Week 1, Intravenous Weeks 2 up to 78, and Repeat-Dose Weeks 1, 2, 3, 4, 5, 6, 7, 8, and 9 (Final/Early Withdrawal).

The following vital signs will be assessed:

- T
- BP
- HR
- RR

Vital signs will be routinely monitored by the study staff as detailed in Appendix 1. The investigator will be required to classify vital signs abnormalities as clinically significant or not according to his/her criteria. Results will be recorded in the subject's source documentation records and eCRF. Vital signs abnormalities judged by the investigator as clinically significant will be considered AEs.

8.2.7 Physical Examinations

A medically certified individual (i.e., medical doctor) will conduct a physical examination (excluding breast and genitourinary examination) at the following visits: Screening and Repeat-Dose Week 9 (Final Visit/Early Withdrawal). The investigator will be required to classify the physical finding abnormalities as clinically relevant or not according to his/her judgment.

Results will be recorded in the subject's source documentation records and eCRF. Physical examinations abnormalities judged by the investigator as clinically significant will be considered AEs.

8.3 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Event and Intercurrent Illnesses

8.3.1 Warnings/Precautions

For complete information on Alpha-1 15% and Liquid Alpha$_1$-PI refer to each respective IB (Alpha-1 15% IB, Liquid Alpha-1 IB).

8.3.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to the IP.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

8.3.3 Adverse Event Definitions

8.3.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily

have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.3.3.2 Suspected Adverse Drug Reactions/Adverse Reactions

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility.

In the framework of this study, a suspected ADR for which there is a reason to conclude that the drug caused the event will be labeled as an adverse reaction (AR); thus, ARs are a subset of suspected ADRs.

An AE will be considered a suspected ADR when either the Sponsor or the investigator considers that the drug might have caused the AE.

8.3.4 Assessment of Causality of Adverse Event

The investigator is required to provide a causality assessment for each AE reported to the Sponsor. The assessment of the causal relationship of an AE to the administration of IP must be a clinical decision based on all available information at the time of the completion of the eCRF and/or SAE form. The Sponsor will consider the investigator's causality assessment and also provide its own assessment.

Causal relationship to the IP will be established according to medical judgment on whether there is a **reasonable possibility of a causal relationship between the AE and the IP administration**.

The investigator must determine and classify the AE causality according to the following categories:

Unrelated/Not related: there is not a reasonable possibility of causal relationship between the AE and the IP.

Possibly related: there is evidence to suggest a causal relationship between the IP and the AE.

Definitely related: there is a reason to conclude that the IP caused the AE.

Criteria to assess the causal relationship should take into account the following conditions: 1) a plausible temporal sequence from the IP administration to the AE onset; 2) whether the event follows a known response pattern to the suspected treatment; 3) whether the AE could be reasonably explained by the subject's clinical state, comorbidities, or concomitant medications, as well as 4) the occurrence of improvement on stopping/reducing the treatment (positive dechallenge) and/or reappearance of the event on repeated exposure (positive rechallenge).

For expedited safety reporting purposes, AEs assessed as either "definitely related" or "possibly related" will be considered POTENTIALLY RELATED or just RELATED.

For any subject, all AEs that occur at any time from the beginning of IP administration until the final visit of the clinical trial will be considered treatment-emergent adverse events (TEAEs). Any AE reported prior to administration of the IP will be considered a non-treatment-emergent adverse event (non-TEAE) and causal relationship will always be "Unrelated/Not related."

8.3.5 Severity of Adverse Event or Suspected Adverse Drug Reaction

Adverse events and suspected ADRs will be classified depending on their severity according to the following definitions:

Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.

Moderate: an AE that interferes with the subject's normal activities.

Severe: an AE that prevents the subject from performing their normal activities.

Adverse event, suspected ADR, and AR severity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate, or severe but not necessarily serious in all these cases.

The investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account current criteria included in this section.

8.3.6 Expectedness of Adverse Event or Suspected Adverse Drug Reaction

An AE, suspected ADR including AR is considered "unexpected" if the nature, seriousness, severity, or outcome of the reaction(s) is not consistent with the reference information. The expectedness shall be determined by the Sponsor according to the reference document (Alpha-1 15% IB, Liquid Alpha-1 IB) for any serious ADRs (possibly related or related SAEs) for expedited safety reporting purposes.

8.3.7 Seriousness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR including AR is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or

hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above).

NOTE: Hospitalization is to be considered only hospital admission (including emergency room stay) for equal or more than 24 hours. The following hospitalizations should not be reported as SAEs:

- Hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol or as part of a routine procedure followed by the center.
- Admissions not associated with an AE (e.g., social hospitalization for the purpose of respite care, survey visits, or annual physicals).
- Elective or pre-planned hospitalizations for a pre-existing condition that had not worsened from Baseline (e.g., elective or scheduled surgery arranged prior to start of the study).

This definition permits either the Sponsor or the investigator to decide whether an event is "serious". If either the Sponsor or the investigator believes that the event is serious, the event must be considered "serious" and evaluated by the Sponsor for expedited reporting.

8.3.8 Adverse Event Documentation

All AEs and SAEs occurring after the subject has **signed the ICF through the end of study** (i.e., Repeat Dose Week 9 Visit [Final Visit/Early Withdrawal Visit]) must be fully recorded in the subject's source documentation records, eCRF, and SAE form (if serious). If no AE has occurred during the study period, this should also be indicated in the subject's source documentation records and eCRF.

It is the responsibility of the investigator to ensure that AEs are appropriately recorded.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded in the subject's source documentation records and the AE eCRF:

- The verbatim term (a diagnosis is preferred)
- Date/time of onset
- Date/time of resolution
- Severity (mild, moderate, severe)
- Causality (unrelated, possibly related, definitely related)*
- Seriousness (yes, no)
- Action taken (with regard to IP)
- Other action (to treat the event)
- Outcome and sequelae (follow-up on AE)

*Causality assessment will be made only when the AE occurs after the subject has initiated at least one infusion of the IP. An AE occurring before subject's exposure to IP will be always labeled as "unrelated".

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE (if applicable), the time of onset of the AE and the time of AE change in intensity and/or resolve will be captured in the subject's source documentation records and eCRF.

In addition to the investigator's own description of the AEs, each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For example, a laboratory test abnormality considered clinically significant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged clinically significant in the context of the subject's medical history by the investigator, should be reported as an AE. Each event must be described in detail along with start and stop dates, severity, relationship to IP, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

8.3.9 Adverse Events of Special Interest

All COPD exacerbations occurring during the study will be recorded. Each subject will be assessed for signs and symptoms of exacerbations at each study visit (Section 8.2.1). Given that COPD exacerbations are part of the natural history of AATD, COPD exacerbations will not be reported as AEs unless a COPD exacerbation meets the criteria of an SAE (Section 8.3.7). If an exacerbation meets criteria for an SAE, it will be reported as such (Section 8.3.10.1), and the standard of care should be followed. Results from standard of care should be obtained and reported.

8.3.10 Reporting of Serious Adverse Events

8.3.10.1 Reporting of Serious Adverse Events

Any SAE (see Section 8.3.7) that occurs after **signing the study ICF through the end of study** (i.e., Repeat-Dose Week 9 [Final Visit/Early Withdrawal]) must be expeditiously reported whether or not considered attributable to the IP. Each SAE must be fully recorded in the subject's source documentation records, eCRF, and SAE Report Form. In addition, any SAE that occurs after the end of study or after study completion due to early termination should be reported only to Grifols Global Pharmacovigilance if the investigator becomes aware of the event and feels that it is related to the use of investigational product.

SAEs will be reported using the designated SAE Report Form. When the investigator becomes aware of an SAE, she/he must submit a completed, signed and dated SAE Report Form (in English) **within 24 hours** to the Sponsor by email/fax. The date of this SAE discovery by the site staff should be documented in the source documents (i.e., medical records).

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow-up, and for the outcome, must also be supplied to the Sponsor in a timely manner (within 3 days from its identification or within 24 hours for

relevant new information) by means of the SAE Report Form. In addition, the Sponsor or contract research organization may request additional information and/or reports.

All SAE Report Forms must be reported to:

Grifols Global Pharmacovigilance
Email: [redacted]
FAX (back-up only): [redacted] (International)

When required, and according to local law and regulations, SAEs must be reported to the IRB and regulatory authorities. Copies of the investigator's reports must be sent to the Sponsor.

8.3.10.2 Reporting Pregnancy

While pregnancy itself is not a true "AE," pregnancy occurring in a clinical study must be followed, to collect information regarding the experiences of gestation and pregnancy with IP exposure. Any female subject who becomes pregnant during the study will be discontinued from IP treatment. The investigator must report any pregnancy that occurs in a female study subject/partner of a male subject subsequent to first exposure to the IP through Repeat-Dose Week 9 (Final/Early Withdrawal Visit) (i.e., end of study).

A pregnancy not verified before enrollment but occurring during the course of the study will not be considered an AE, unless a relation to the IP is suspected. In any case, a *Pregnancy Report Form* must be completed and sent as soon as possible to the Sponsor. A copy of the form should be filed at the study site for follow-up until the end of the pregnancy. Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect observed in the child must be reported as an SAE within 24 hours of the investigator or study personnel's first knowledge.

Please use the email address or fax numbers (back up only) in Section 8.3.10.1 for reporting pregnancy.

8.3.11 Internal Safety Review Committee

An internal safety review committee (iSRC), comprised of impartial and independent members at least the Grifols medical monitor or qualified medical designee, pharmacovigilance, and a third individual of the study team such as someone knowledgeable in the epidemiological field or, knowledgeable in the therapeutic area, or a statistician will be established to monitor the progress and the safety of the clinical trial participants, as well as any pump related issues. The iSRC charter will outline the composition, responsibilities, schedule of the iSRC meetings, and study stopping rules. At a minimum, the iSRC will convene to review subject data, including but not limited to demographics, dosing, concomitant medications, hematology and chemistry, and adverse events to confer and document agreement that the next dose level is considered appropriate and safe.

The first Cohort will include approximately 8 subjects receiving the 72 mg/kg (Cohort 1) starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). To ensure

subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose), safety data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (60 mg/kg for Cohort 1) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 1 (72 mg/kg dose) for all subjects will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 1. Following completion of Treatment Period 2 (Repeat-Dose) for subjects in Cohort 1, the iSRC will evaluate safety data prior to initiating Cohort 2 (180 mg/kg). Dosing must not commence to Cohort 2 until Grifols has provided written confirmation to the PI. If the iSRC determines it is safe to proceed with dose escalation, Cohort 2 will be initiated.

The second cohort will include approximately 8 subjects receiving the 180 mg/kg (Cohort 2) dose of Alpha-1 15% starting with a single-dose of Alpha-1 15% in Treatment-Period 1 (Single-Dose). Furthermore, enrollment into Cohort 2 will only commence once the iSRC has reviewed safety data from the entire cohort of subjects treated with 72 mg/kg. **Subjects cannot enroll into both cohorts**. To ensure subjects' safety, after a subject completes Treatment Period 1 (Single-Dose) and the Washout/Serial PK phase, the subject will enter into the Single-Dose Data Evaluation Phase where Liquid Alpha$_1$-PI will be administered, and PK samples obtained. Once all subjects have completed Treatment Period 1 (Single-Dose) phase, safety data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) will be evaluated by the iSRC to determine if subjects may proceed to Treatment Period 2 (Repeat-Dose). During the Single-Dose Data Evaluation phase, Liquid Alpha$_1$-PI (licensed as Prolastin®-C Liquid) weekly IV Infusions (120 mg/kg for Cohort 2) will be administered, with the last IV dose given 1 week prior to the first repeat SC dose. PK data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) from a subset of subjects will be evaluated by the study team to determine/confirm the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 2.

In addition to the DLT and study stopping rules, individual stopping rules that would include positive testing for immunogenicity and severe infusion site reactions causing the subject to prematurely discontinue the study will be implemented. Stopping rules will be based on safety outcomes in cases where infusion site reactions emerge at unexpectedly high or severe levels or a subject is deemed positive for immunogenicity.

8.4 Type and Duration of the Follow-Up of Subjects after Adverse Events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected, and the investigator decides that no further follow-up is necessary.

Any SAE that occurs after the end of the clinical study or after study completion due to early termination will not be actively collected. However, if such cases are reported by the investigator as related to the study treatment, they will be entered into the safety database for expedited purposes.

9 STATISTICS

9.1 Statistical Methods

Unless otherwise specified, descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data.

In general, the single-dose and repeat-dose SC regimens at the same dose level will be considered different treatment groups in data analyses. Repeat weekly IV infusions of 60 mg/kg or 120 mg/kg Liquid Alpha$_1$-PI will be additional treatment groups of interest in this study.

Data handling and evaluation procedures will be described in the Statistical Analysis Plan (SAP).

9.1.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment cohort and overall. For quantitative variables, mean, SD, median, and minimum/maximum will be provided. For qualitative variables, the frequency and percentage will be provided.

9.1.2 Safety Analysis

Safety analyses will be performed on the safety population. Safety analyses will be addressed by listing and tabulation of AEs (including suspected ADRs and ARs), infusion site reactions (to be reported as AEs), COPD exacerbations, laboratory tests, PFTs, vital signs, and physical assessments. Data will be summarized using descriptive analyses and treatment comparisons will be based on review of descriptive statistics.

9.1.2.1 Adverse Events

Adverse events will be coded and classified using MedDRA terms (system organ class and preferred term).

When the causal relationship of an AE is classified by the investigator as definitely or possibly related, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definitely related" will be defined as an AR. The Sponsor will consider the investigator's causality assessment and also provide its own assessment. If there is any disagreement in the causality assessment between the investigator and the Sponsor, a separate summary of suspected ADRs/ARs will be provided.

For summary purposes, AEs will be classified as TEAEs or non-TEAEs depending on the comparison of AE onset date/time with the start date/time of study treatment. A TEAE will be defined as an AE which occurs between the start of study treatment and the final visit of the clinical study. A non-TEAE will be defined as an AE which occurs prior to the start of study treatment. Non-TEAEs and TEAEs will be summarized separately. Treatment-emergent adverse events will be further attributed to a treatment by comparing the TEAE onset date/time to the start date/time of the first infusion in each treatment period.

In addition, TEAEs, suspected ADRs, and ARs will be summarized by treatment group, system organ class, preferred term, causal-relationship, severity, toxicity grade (if applicable), and seriousness (serious vs non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe AE or the AE with the strongest causal relationship. Summaries will also be provided for the total number of events and the rate per infusion.

Temporally-associated AEs defined as those events occurring during or within 72 hours following the end of the IP infusion will be separately summarized by presenting infusion/subject incidences and rates/percentages. In addition, local infusion site reactions will be summarized.

Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be individually listed.

All COPD exacerbations will be listed and summarized by treatment.

9.1.2.2 Clinical Laboratory Values Including Immunogenicity Testing

All clinical laboratory data will be listed for each subject and summarized. The original value and the change from baseline will be summarized for numeric results and frequency/percentage will be summarized for qualitative results. For laboratory tests with normal ranges, out of normal range values will be flagged and shift tables will be provided.

All immunogenicity results will be listed, and new positive immunogenicity results will be tabulated.

The investigator will be required to classify out of the normal range laboratory results reported by the laboratory as clinically significant or not according to his/her criteria.

Out of the normal range laboratory results judged by the investigator as clinically significant in the context of the subject's medical history will be considered AEs.

9.1.2.3 Vital Signs

Vital signs (HR, BP, RR, T) will be listed for each subject and summarized. The original value and the change from baseline will be summarized for numeric results.

Clinically significant vital signs abnormalities will be presented as AEs. Clinical relevance will be based on the investigator's judgment.

9.1.2.4 Pulmonary Function Tests

Pulmonary function tests (FEV_1 [absolute and predicted] and FVC) will be listed for each subject and summarized. The original value and the change from baseline will be summarized for numeric results.

9.1.2.5 Physical Assessment

Physical assessment findings (normal or abnormal) will be listed for each subject and summarized. Any clinically significant abnormalities developed by a subject during the clinical study and not already present at baseline will be reported as AEs. Clinical relevance will be based on the investigator's judgement.

9.1.3 Pharmacokinetic (PK) Analysis

Calculation of PK parameters:

PK parameters will be calculated using non-compartmental methods.

PK parameters for SC administration of Alpha-1 15%:

The single-dose PK parameters of $Alpha_1$-PI of Alpha-1 15% in subjects with AATD will be evaluated. The PK profiles of $Alpha_1$-PI following the single dose at Single-Dose Week 1 will be characterized by PK parameters, including $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $\%AUC_{ex}$, $AUC_{0\text{-}7\ days}$, C_{max}, t_{max}, $t_{1/2}$, CL, and V_d, based on $Alpha_1$-PI concentrations as measured by antigenic content as well as functional activity assays.

In addition, the steady-state PK parameters of $Alpha_1$-PI from weekly SC administration of Alpha-1 15% in subjects with AATD will be evaluated. The PK profiles of $Alpha_1$-PI following the last repeat dose at Repeat-Dose Week 8 will be characterized by PK parameters, including $AUC_{0\text{-}7\ days}$, C_{max}, t_{max}, $t_{1/2}$, CL, V_d, accumulation ratio, and time-invariance ratio, based on $Alpha_1$-PI concentrations as measured by antigenic content as well as functional activity assays. Mean trough will be calculated as the average value of the trough $Alpha_1$-PI concentrations measured at Repeat-Dose Weeks 6, 7, 8, and 9 (Final/Early Withdrawal Visit).

NOTE: if the dosing interval (τ) for the repeat-dose SC regimen is different from weekly (i.e., 7 days), the calculation of mean trough above will be adjusted to use appropriate trough samples only, and $AUC_{0\text{-}\tau}$ will be calculated in place of $AUC_{0\text{-}7\ days}$.

For all single-dose and repeat-dose SC PK parameters, except t_{max}, the baseline-corrected values will also be calculated, where baseline is the endogenous $Alpha_1$-PI concentration measured at Single-Dose Week 5 (4 weeks after the single SC infusion at Single-Dose Week 1).

PK parameters for IV administration of Liquid $Alpha_1$-PI:

The steady-state PK parameters of $Alpha_1$-PI from weekly IV administration of Liquid $Alpha_1$-PI in subjects with AATD will be evaluated. The PK profiles of $Alpha_1$-PI following the 8^{th} weekly IV infusion at Intravenous Week 8 will be characterized by PK parameters, including $AUC_{0\text{-}7\ days}$, C_{max}, t_{max}, $t_{1/2}$, CL, V_d, based on $Alpha_1$-PI concentrations as measured by antigenic content as well as functional activity assays. Mean trough will be calculated as

the average value of the trough Alpha$_1$-PI concentrations measured at Intravenous Weeks 8 and 9.

For all IV PK parameters, except t_{max}, the baseline-corrected values will also be calculated, where baseline is the endogenous Alpha$_1$-PI concentration measured at Single-Dose Week 5/Intravenous Week 1 (4 weeks after the single SC infusion at Single-Dose Week 1).

Analyses of PK concentrations and derived PK parameters:

Alpha$_1$-PI concentrations at each time point and all PK parameters will be listed and summarized by treatment using descriptive statistics including n, mean, standard deviation (SD), percent coefficient of variation (%CV), median, minimum, and maximum. Geometric mean and 90% CI for the geometric mean will also be calculated for all PK parameters (except t_{max}). Data listing will include the Alpha$_1$-PI concentrations (both antigenic content and functional activity assays) at each time point as well as the corrected concentrations where the correction is performed by subtracting the Single-Dose Week 5/Intravenous Week 1 measurements (after 4-week washout following the end of dosing at Single-Dose Week 1) from the uncorrected concentrations at each time point.

Dose proportionality will be separately assessed for single-dose and repeat-dose SC administrations by comparing dose-normalized SC PK parameters between the 72 mg/kg and 180 mg/kg dose levels.

The impact of the volume and duration of infusion on the PK endpoints following SC administration will be evaluated by using a linear regression model fitting natural log-transformed SC PK parameters as the response variable and volume and duration of infusion as the explanatory variables.

To compare the steady-state PK between the IV administration (in the Single-Dose Data Evaluation Period) and SC administration (in Treatment Period 2), natural log-transformed AUC (normalized to the same dose interval, if necessary) and C_{max} values will be analyzed by analysis of variance with a mixed-effect model. The model will include treatment (repeat-dose Alpha-1 15% or repeat-dose Liquid Alpha$_1$-PI) as a fixed effect, and subject as a random effect. From this model, the geometric least-squares mean ratio between Alpha-1 15% and Liquid Alpha$_1$-PI and the corresponding 90% CI will be calculated.

Analysis of the Single-Dose PK and Safety Data prior to Repeat-Dose:

In each cohort, the single-dose PK data from Treatment Period 1 (Single-Dose) will be summarized using appropriate descriptive statistics as described above during the Single-Dose Data Evaluation Period. The analysis results will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose). Safety data will be summarized for all subjects.

9.1.4 Exploratory Analysis

The exploratory endpoint of subject satisfaction with SC treatment via a written questionnaire following Treatment Period 2 (Repeat-Dose) will be listed and summarized using descriptive statistics appropriate to the endpoint.

9.2 Determination of Sample Size

No formal power/sample size calculations were performed. The sample size for each cohort is primarily based on feasibility. A sample size of 8 Alpha-1 15% subjects per cohort is deemed sufficient to address the safety and PK objectives of this early phase, dose escalation study.

9.3 Level of Significance to Be Used

The hypothesis testing for the PK comparisons will be performed at a two-sided alpha level of 0.10 or a one-sided alpha level of 0.05. When applicable, all other statistical inferences will be tested at a two-sided alpha level of 0.05, unless otherwise specified.

9.4 Criteria for Termination of the Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) when required.

9.5 Procedure for Accounting for Missing, Unused, and Spurious Data (if applicable)

The procedure for accounting for missing, unused, and spurious data (if applicable) will be detailed in the SAP.

9.6 Reporting Deviation(s) from the Statistical Analysis Plan

The detailed statistical analysis methodologies will be documented in the SAP. If there are any deviations from the originally planned analyses in the SAP, they will be fully described and justified in the protocol amendment(s) and/or final Clinical Study Report.

9.7 Subject Population(s) for Analysis

The safety population will include all subjects who receive any dose of IP (Alpha-1 15% or Liquid Alpha$_1$-PI) and will be used for safety analyses.

The PK population will include all subjects who receive IP and had sufficient and valid Alpha1-PI concentration data to allow the calculation of PK parameters. Pharmacokinetic analyses will be based on this population.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data will be recorded and kept current in CRF/eCRFs by the study site personnel directly responsible for the information and reviewed for completeness by the monitor. Grifols personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRF/eCRFs for consistency and to verify adherence to the protocol, and the completeness, consistency, and accuracy of data entered. "Source documentation" includes individual subject files, separate from the CRF/eCRFs, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, investigational product dispensing logs, and other notes as appropriate. The investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring and auditing procedures defined/agreed by the Sponsor will be followed, in order to comply with ICH GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, ICH GCP and legal aspects. The on-site verification of the CRF/eCRF for completeness and clarity will include cross checking with source documents, and clarification of administrative matters. Query verification of data will be described in the Data Management Plan.

Representatives of regulatory authorities or of Grifols may conduct audits or inspections or audits of the investigator study site. If the investigator is notified of an audit or inspection by a regulatory authority, the investigator agrees to notify the Grifols Representative (e.g., CAM, PM, PL) immediately. The investigator agrees to provide to representatives of a Regulatory Agency or Grifols access to records, facilities, and personnel for the effective conduct of an audit or inspection.

12 ETHICS

12.1 Institutional Review Board

Documented approval from appropriate IRBs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRBs approval must be obtained and also forwarded to the Sponsor. The IRBs must supply to the Sponsor, upon request, a list of the IRBs members involved in the vote and a statement to confirm that the IRB is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

12.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the Sponsor representatives and/or an inspection by Regulatory Authority representatives at any time. The investigator must agree to the audit or inspection of study-related records by the Sponsor representatives and/or

Regulatory Authority representatives, and must allow direct access to source documents to the Sponsor and/or Regulatory Authority representatives.

Modifications to the study protocol will not be implemented by either the Sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

No medical waivers for protocol inclusion/exclusion criteria will be allowed by the Sponsor. If there is a need for changes to the protocol inclusion/exclusion criteria, the protocol will be amended to include such changes. The protocol amendment will be submitted to the competent regulatory authority and/or IRB as applicable per regulations, which allows implementation of the revised inclusion/exclusion criteria in the study.

12.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

12.4 Subject Information and Consent

Subject information and ICF will be provided to investigator sites. Prior to the beginning of the study, the investigator must have the IRB written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the IRB together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to Sponsor by the investigator site.

Written ICF must be obtained before any study specific procedure takes place. Participation in the study and date of ICF given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF will be provided to the subject or subject's authorized representative.

12.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject code number will be recorded in the CRF/eCRF, and if the subject's name appears on any other document (e.g., pathologist report), it must be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the Sponsor, IRB, or Regulatory Authorities may inspect their medical records and personal health

information to verify the information collected, and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Handling

The study data will be recorded and kept current in the CRF/eCRF by the site study personnel directly responsible for the information. Entries made in the CRF/eCRF must be verifiable against source documents. The data in the CRF/eCRF will be monitored at the site by Grifols representatives at regular intervals and reviewed for completeness and compared with the source documents. Examples of acceptable source documents include individual subject medical records, prospective information gathered on source documentation worksheets, lab reports and other diagnostics pertinent to this study which are separate from the CRF/eCRFs. The list of types of source documents which will be defined in the source data agreement will be kept in the study files at the Sponsor and at the investigator sites.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE form. The SAE form must be kept in site records with a copy provided to the designated person as detailed in the study file.

13.2 Record Retention

At study completion, all study data will be transferred to Grifols according to ICH GCP guidelines, local laws, regulations, and Grifols requirements. The study file and all source data should be retained until notification is given by the Sponsor for destruction.

An investigator is required by ICH GCP guidelines to retain the study files. If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (e.g., other investigator). Grifols must be notified in writing of the person responsible for record retention and the notification will be retained in the Sponsor study file and the investigator site file.

14 FINANCING AND INSURANCE

In the event of subject injury as a direct result of either administration of investigational product or any non-standard of care study procedure, Sponsor will pay for the costs of treatment, provided the subject has followed the instructions given by the study doctor and the illness or injury is not due to the natural progression of any conditions existing before the subject participated in the study. Financial compensation for such things as lost wages, disability, or discomfort due to any research-related injury is not available.

Sponsor shall maintain comprehensive general liability insurance or self-insurance in amounts adequate to cover any damage, demand, claim, loss or liability caused or incurred by Sponsor, or as otherwise required by applicable laws and/or regulations.

15 PUBLICATION POLICY

Institution and the investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all appropriates sites. If such a multi-center publication is not submitted within 12 months after conclusion of the study at all sites or after Grifols confirms there will be no joint, multi-center publication, then institution and/or investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or investigator shall furnish Grifols with a copy of any proposed publication at least thirty (30) days in advance of the date of submission for publication.
- Within said thirty (30) day period, Grifols shall:
  - Review such proposed publication for Confidential Information (other than Study results) and for subject information subject to the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and other applicable privacy laws;
  - Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
  - By written notice to the investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains Confidential Information, protected subject information, or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and
  - By written request, Grifols may delay proposed publications up to sixty (60) days to allow Grifols to protect its interests in Grifols Inventions described in such publications.
- Institution and/or investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

16 REFERENCES

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CONFIDENTIAL

17 APPENDICES

APPENDIX 1 SCHEDULE OF STUDY PROCEDURES AND EVENTS

Study Period	Screening Period	Treatment Phase [a]												Follow-up Phase [a,b]
Study Period	Screening	Treatment Period 1 & Washout/Serial PK				Single-Dose Data Evaluation Period				Treatment Period 2				Follow-up
Visit Number	Screening[c]	SD-WK 1	SD-WK 2	SD-WK 3 & 4	SD-WK 5 / IV-WK 1	IV-WK 2 to IV-WK 7	IV-WK 8	IV-WK 9	IV-WK 10 up to 78	RD-WK 1	RD-WK 2, 3 & 4	RD-WK 5, 6 & 7	RD-WK 8	RD-WK 9
Time Period or Infusion Number	Day -30 to Day -1	SD-SC# 1	Washout 1/ Serial PK	Washout 2 & 3/ Serial PK	IV#1	IV#2 to IV#7	IV#8	IV#9	IV#10 up to IV#78	RD-SC# 1	RD-SC# 2, 3 & 4	RD-SC# 5, 6 & 7	RD-SC# 8	Final Visit / Early Withdrawal
Visit Location	Study Site	Study Site	Study Site	Study/ Alternate Site[d]	Study Site	Study/ Alternate Site[d]	Study Site	Study Site	Study/ Alternate Site[d]	Study Site	Study Site	Study/ Alternate Site[d]	Study Site	Study Site
Procedures and Assessments														
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Assign subject number	X													
Medical history and demography	X													
Washout of prior augmentation therapy	X													
COPD exacerbation assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local infusion site reactions assessment		X	X	X						X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening Period	Treatment Phase [a]												Follow-up Phase [a,b]
Study Period	**Screening**	**Treatment Period 1 & Washout/Serial PK**				**Single-Dose Data Evaluation Period**				**Treatment Period 2**				**Follow-up**
Visit Number	**Screening[c]**	**SD-WK 1**	**SD-WK 2**	**SD-WK 3 & 4**	**SD-WK 5 / IV-WK 1**	**IV-WK 2 to IV-WK 7**	**IV-WK 8**	**IV-WK 9**	**IV-WK 10 up to 78**	**RD-WK 1**	**RD-WK 2, 3 & 4**	**RD-WK 5, 6 & 7**	**RD-WK 8**	**RD-WK 9**
Time Period or Infusion Number	**Day -30 to Day -1**	**SD-SC# 1**	**Washout 1/ Serial PK**	**Washout 2 & 3/ Serial PK**	**IV#1**	**IV#2 to IV#7**	**IV#8**	**IV#9**	**IV#10 up to IV#78**	**RD-SC# 1**	**RD-SC# 2, 3 & 4**	**RD-SC# 5, 6 & 7**	**RD-SC# 8**	**Final Visit / Early Withdrawal**
Visit Location	**Study Site**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**
Procedures and Assessments														
Physical examination (including height at Screening only)[g]	X													X
Weight	X	X[h]			X[h]					X[h]				
Pre- and Post-bronchodilator PFTs (FEV_1 [absolute and predicted] and FVC)	X				X					X	X[u]			X
$Alpha_1$-PI concentration for diagnosis of AATD (if needed)	X													
Genotyping/phenotyping for AATD (if needed)[i]	X													
Chemistry, hematology, and urinalysis	X				X					X				X
Collection of virus safety retain samples[j]	X	X			X					X	X[u]	X[k]		X

Study Period	Screening Period	Treatment Phase [a]												Follow-up Phase [a,b]
Study Period	**Screening**	**Treatment Period 1 & Washout/Serial PK**				**Single-Dose Data Evaluation Period**				**Treatment Period 2**				**Follow-up**
Visit Number	**Screening[c]**	**SD-WK 1**	**SD-WK 2**	**SD-WK 3 & 4**	**SD-WK 5 / IV-WK 1**	**IV-WK 2 to IV-WK 7**	**IV-WK 8**	**IV-WK 9**	**IV-WK 10 up to 78**	**RD-WK 1**	**RD-WK 2, 3 & 4**	**RD-WK 5, 6 & 7**	**RD-WK 8**	**RD-WK 9**
Time Period or Infusion Number	**Day -30 to Day -1**	**SD-SC# 1**	**Washout 1/ Serial PK**	**Washout 2 & 3/ Serial PK**	**IV#1**	**IV#2 to IV#7**	**IV#8**	**IV#9**	**IV#10 up to IV#78**	**RD-SC# 1**	**RD-SC# 2, 3 & 4**	**RD-SC# 5, 6 & 7**	**RD-SC# 8**	**Final Visit / Early Withdrawal**
Visit Location	**Study Site**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**
Procedures and Assessments														
Collection of samples for immunogenicity testing[m]		X			X					X	X[l,u]			X
Urine pregnancy test[n]	X	X			X					X				X
Urine cotinine	X													X
Vital signs (HR, BP, RR, and T)		X[o]			X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X
Pre-infusion blood sample for alpha1-PI concentration		X[f]					X[f]				X[l]	X[k,p]	X[f,p]	
IP infusion		X			X	X	X	X	X	X	X	X	X	
Administer subject satisfaction with SC treatment questionnaire														X
Blood sample for Alpha1-PI concentration within 5 minutes following completion of last infusion		X					X						X	

Study Period	Screening Period	Treatment Phase [a]												Follow-up Phase [a,b]
Study Period	Screening	Treatment Period 1 & Washout/Serial PK				Single-Dose Data Evaluation Period				Treatment Period 2				Follow-up
Visit Number	Screening[c]	SD-WK 1	SD-WK 2	SD-WK 3 & 4	SD-WK 5 / IV-WK 1	IV-WK 2 to IV-WK 7	IV-WK 8	IV-WK 9	IV-WK 10 up to 78	RD-WK 1	RD-WK 2, 3 & 4	RD-WK 5, 6 & 7	RD-WK 8	RD-WK 9
Time Period or Infusion Number	Day -30 to Day -1	SD-SC# 1	Washout 1/ Serial PK	Washout 2 & 3/ Serial PK	IV#1	IV#2 to IV#7	IV#8	IV#9	IV#10 up to IV#78	RD-SC# 1	RD-SC# 2, 3 & 4	RD-SC# 5, 6 & 7	RD-SC# 8	Final Visit / Early Withdrawal
Visit Location	Study Site	Study Site	Study Site	Study/ Alternate Site[d]	Study Site	Study/ Alternate Site[d]	Study Site	Study Site	Study/ Alternate Site[d]	Study Site	Study Site	Study/ Alternate Site[d]	Study Site	Study Site
Procedures and Assessments														
Blood samples for Alpha1-PI concentration at 15 and 30 min, 1, 2, 4, and 8 hrs, and 1, 2, and 5 days following completion of last infusions[q]							X[e]							
Blood samples for Alpha1-PI concentration at 1, 4, and 8 hrs, and 1, 2, 3, 4, 5, and 6 days following completion of last infusion[q]		X[e]											X[e]	
Blood sample for Alpha1-PI concentration 7 days following completion of last infusion[q]			X					X[r]						X[r]

Study Period	Screening Period	Treatment Phase [a]												Follow-up Phase [a,b]
Study Period	**Screening**	**Treatment Period 1 & Washout/Serial PK**				**Single-Dose Data Evaluation Period**				**Treatment Period 2**				**Follow-up**
Visit Number	**Screening[c]**	**SD-WK 1**	**SD-WK 2**	**SD-WK 3 & 4**	**SD-WK 5 / IV-WK 1**	**IV-WK 2 to IV-WK 7**	**IV-WK 8**	**IV-WK 9**	**IV-WK 10 up to 78**	**RD-WK 1**	**RD-WK 2, 3 & 4**	**RD-WK 5, 6 & 7**	**RD-WK 8**	**RD-WK 9**
Time Period or Infusion Number	**Day -30 to Day -1**	**SD-SC# 1**	**Washout 1/ Serial PK**	**Washout 2 & 3/ Serial PK**	**IV#1**	**IV#2 to IV#7**	**IV#8**	**IV#9**	**IV#10 up to IV#78**	**RD-SC# 1**	**RD-SC# 2, 3 & 4**	**RD-SC# 5, 6 & 7**	**RD-SC# 8**	**Final Visit / Early Withdrawal**
Visit Location	**Study Site**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**	**Study/ Alternate Site[d]**	**Study Site**	**Study Site**
Procedures and Assessments														
Blood sample for Alpha1-PI concentration 14 and 21 days (i.e., 2 and 3 weeks) following completion of SD-SC#1 infusion[q]				X										
Blood sample for Alpha1-PI concentration 28 days (i.e., 4 weeks) following completion of SD-SC#1 infusion[q]					X[s]									
Blood sample for Alpha1-PI concentration at the Early Withdrawal Visit														X
Biomarker Retains[t]		X								X				X
Dispense IP		X			X					X	X	X	X	

AATD: Alpha1-antitrypsin deficiency; Alpha1-PI: Alpha1-Proteinase Inhibitor; AE: adverse event; BP: blood pressure; COPD: chronic obstructive pulmonary disease; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; HR: heart rate; IP: investigational product; IV: intravenous;

PFTs: pulmonary function tests; PK: pharmacokinetic; RD: repeat-dose; RR: respiratory rate; SC: subcutaneous; SD: single-dose; T: temperature; WK: week.

[a] Weekly visits should be scheduled at the protocol specified week relative to the date of the Week 1 Visit of each period; a + 1 day window is allowed.

[b] Subjects must not receive any Alpha$_1$-PI augmentation therapy, including the IPs for this study, during the Washout/Serial PK period (between Single-Dose Week 1 and Single-Dose Week 5/Intravenous Week 1) and between Repeat-Dose Weeks 8 and 9 (Final/Withdrawal Visit).

[c] The Screening Visit must occur up to 30 days prior to the Single-Dose Week 1 (Baseline) Visit.

[d] Procedures/assessments for indicated visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

[e] Treatment Period 1 & Washout/Serial PK: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, 3, 4, 5, and 6 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

Single-Dose Data Evaluation: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, and 5 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

Treatment Period 2: To facilitate the collection of serial PK blood samples, samples for Alpha$_1$-PI concentration taken at 8 hours and 1, 2, 3, 4, 5, and 6 days following completion of last infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

[f] Must be performed within 25 minutes prior to initiation of infusion.

[g] Excludes breast and genitourinary exam.

[h] For Single-Dose Week 1, the recorded weight will be used to calculate the IP infusion dose for Treatment Period 1. For Single-Dose Week 5/Intravenous Week 1, the recorded weight will be used to calculate the IP infusion dose for the Single-Dose Data Evaluation Period. For Repeat-Dose Week 1, the recorded weight will be used to calculate the IP infusion dose for Treatment Period 2.

[i] A blood sample for genotyping/phenotyping is required only if the genotype has not yet been documented. Note: The laboratory tests will not detect "at-risk" alleles and prior documentation must exist in the subject's medical records.

[j] Collection of samples for viral NAT and viral serology retention.

[k] Sample pre-infusion Alpha$_1$-PI concentration collected at Repeat-Dose Weeks 6 and 7. Collection of virus safety retain samples are collected at Repeat-Dose Week 7 only and NOT collected at Repeat-Dose Weeks 5 or 6.

[l] Sample collected at Repeat-Dose Week 4 only. Collect but test only if deemed appropriate (e.g., unexpected PK profile).

[m] If a subject has a positive ADA response that would require follow-up testing to determine if the result is a transient or sustained response, additional blood samples may be collected for a time period of up to 1 year following the positive ADA response. Furthermore, aliquots of immunogenicity samples will be retained for up to 5 years post-study for possible future analysis.

[n] Potential child-bearing females only; results must be negative to participate in the study or continue on IP.

[o] SC Phases: Vital signs must be done within 30 minutes prior to initiation of IP infusion, 30 minutes (± 5 minutes) after initiation of the infusion, and within 30 minutes after completion of the infusion. IV Phases: Vital signs must be done within 30 minutes prior to initiation of IP infusion, within 10 minutes after initiation of the infusion, and within 30 minutes after completion of the infusion (after NaCl flush).

[p] Sample for steady-state trough $Alpha_1$-PI measurement.

[q] PK samples are collected 5 minutes following completion time of SC infusion, 1 hour (± 15 minutes), 4 hours (± 30 minutes), 8 hours (± 2 hours), and 1, 2, 3, 4, 5, 6, 7, 14, 21, and 28 days. A ± 4 hours window is allowed for blood samples taken at 1, 2, 3, 4, 5, and 6 days following completion of the last infusion; a + 1 day window is allowed for blood samples taken at 7, 14, 21, and 28 days following completion of the last infusion. Samples at 14, 21, and 28 days are only collected following completion of Single-Dose Week 1 infusion.

[r] For Intravenous Week 9 and Repeat-Dose Week 9 there will be only 1 blood sample drawn to serve as the serial PK sample at 7 days following completion of the last infusion and as a trough $Alpha_1$-PI measurement.

[s] The blood sample drawn at Single-Dose Week 5/Intravenous Week 1 will be tested for endogenous $Alpha_1$-PI concentration 28 days following completion of the Single-Dose Week 1 infusion (Note: sample is considered the last single-dose serial PK sample; in addition, it will be used to calculate the baseline-corrected PK parameters of $Alpha_1$-PI for both single-dose and repeat-dose SC administrations as well as for repeat-dose IV administration).

[t] Biomarker sample collection is optional (subject may opt out). If a subject opts out of this collection, samples will not be collected, processed, or shipped for storage. Samples will be collected prior to the administration of IP at Week 1 (Baseline).

[u] Collected at ***Repeat-Dose Week 4 only***.

APPENDIX 2 ALPHA1-ANTITRYPSIN DEFICIENCY "AT RISK" ALLELES

Allele	Base[a]	Exon[b]	Mutation
F	M1(Val213)	III	Ard223 CGT → Cys TGT
Z	M1(Ala213)	V	Glu342 GAG → Lys AAG
T	M2	III	Glu264 GAA → Val GTA
S	M1(Val213)	III	Glu264 GAA → Val GTA
M heerlen	M1(Ala213)	V	Pro369 CCC → Leu CTC
M malton	M2	II	Phe52 TTC → Delete
M mineral springs	M1(Ala213)	II	Gly67 GGG → Glu GAG
M procida	M1(Val213)	II	Leu41 CTG → Pro CCG
W bethesda	M1(Ala213)	V	Ala336 GCT → Thr ACT
I	M1(Val213)	II	Arg39 CGC → Cys TGC
M palermo	M1(Val213)	II	Phe51 TTC → Delete
M nichinan	M1(Val213)	II	Phe52 TTC → Delete/Gly148 GGG → Arg AGG
P lowell	M1(Val213)	III	Asp256 GAT → Val GTT
P duarte	M4	III	Asp256 GAT → Val GTT
S iiyama	M1(Val213)	II	Phe53 TTC → Ser TCC
Z augsburg	M2	V	Glu342 GAG → Lys AAG

[a] Indicates the base allele

[b] Indicates in which exon the mutation is located

APPENDIX 3 SUMMARY OF CHANGES FROM VERSION 6.0 TO VERSION 7.0

(Note: Administrative changes including minor administrative corrections are not included in Protocol Summary of Changes)

Sections	**Change From:** **(Version 6.0, dated 25 Oct 2023)** (Strikethrough is added to highlight deleted text)	**Change To:** **(Version 7.0)** (Underline is added to highlight new text)	**Rationale:**
Title page; Sponsor signatories	[redacted]	[redacted]	Sponsor signatory for the role of Sr. VP has been updated due to administrative changes.
Synopsis, 4.2, 7.4.1.3, and 8.3.11	PK data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) ~~for all subjects~~ will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 2.	PK data from Treatment Period 1 (Single-Dose) of Cohort 2 (180 mg/kg dose) <u>from a subset of subjects</u> will be evaluated by the study team to determine/confirm the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose) of Cohort 2.	This is an administrative change. The phrase "for all subjects" is globally replaced with "<u>from a subset of subjects</u>" because the PK data from all Cohort 2 Single-Dose subjects are not necessary to initiate Repeat-Dose in the context of comprehensive PK analyses from the prior Cohort 1 and the increased maximal dose conversion factor of 1.5 which is already established. As such, all PK data from Single-Dose Cohort 2 are not needed for preliminary PK modeling and simulations.
9.1.3	**<u>Analysis of the Single-Dose PK and Safety Data prior to Repeat-Dose</u>**: In each cohort, the single-dose PK ~~and safety~~ data from Treatment Period 1 (Single-Dose) ~~for all subjects~~ will be summarized using appropriate descriptive statistics as described above during the Single-Dose Data Evaluation	**<u>Analysis of the Single-Dose PK and Safety Data prior to Repeat-Dose:</u>** In each cohort, the single-dose PK data from Treatment Period 1 (Single-Dose) will be summarized using appropriate descriptive statistics as described above during the Single-Dose Data Evaluation Period. The analysis	This is an administrative change. The phrase "for all subjects" is removed because the PK data from all Cohort 2 Single-Dose subjects are not necessary to initiate Repeat-Dose in the context of comprehensive PK analyses from the prior Cohort 1 and the increased maximal dose conversion factor of 1.5

Sections	**Change From:** **(Version 6.0, dated 25 Oct 2023)** (Strikethrough is added to highlight deleted text)	**Change To:** **(Version 7.0)** (Underline is added to highlight new text)	**Rationale:**
	Period. The analysis results will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose).	results will be evaluated by the study team to determine the most appropriate repeat-dose regimen for Treatment Period 2 (Repeat-Dose). <u>Safety data will be summarized for all subjects.</u>	which is already established. As such, all PK data from Single-Dose Cohort 2 are not needed for preliminary PK modeling and simulations.