STATISTICAL ANALYSIS PLAN

Aralast NP and Glassia
PHASE 3/4

A Stage 1, Prospective, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Alpha1-Proteinase Inhibitor (A1PI) Augmentation Therapy in Subjects with A1PI Deficiency and Chronic Obstructive Pulmonary Disease (COPD)

PROTOCOL IDENTIFIER: 460503

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SIGNATURE PAGE

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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ABBREVIATIONS

6MWT	6-minute walk test
A1PI	Alpha1-Proteinase Inhibitor
AE	Adverse Event
APE	Acute Pulmonary Exacerbation
BMI	Body Mass Index
BODE	Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index
BW	Body Weight
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
DL_{CO}	Diffusing Capacity of Carbon Monoxide
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
FEV_1/FVC	Percentage of Vital Capacity Expired in the First Second of Maximal Expiration
FVC	Forced Vital Capacity
HRQoL	Health-Related Quality of Life
IC	Inspiratory Capacity
IgA	Immunoglobulin A
ITT	Intent-to-Treat
IP	Investigational Product
IV	Intravenous
LRTI	Lower Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
MMRC	Modified Medical Research Council
QTcB	QT Interval Corrected for Heart Rate Using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
SAP	Statistical Analysis Plan
SF-36	Short Form (36) Health Survey
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
TEAE	Treatment-Emergent Adverse Event
TLC	Total Lung Capacity
WHO	World Health Organization

1. INTRODUCTION

This is a pilot study to assess the safety and efficacy of alpha1-proteinase inhibitor (A1PI) augmentation therapy in subjects with emphysema/chronic obstructive pulmonary disease (COPD) associated with severe congenital A1PI deficiency with endogenous plasma A1PI level of < 8 μM and documented A1PI genotypes of Pi*Z/Z, Pi*Z/null, Pi*Malton/Z, Pi*Null/Null, or other rare genotypes (except PI*MS, PI*MZ, or PI*SZ). Intravenous (IV) ARALAST NP and GLASSIA augmentation therapy administered as an IV infusion at 60 mg/kg body weight (BW)/week or 120 mg/kg BW/week was to be compared to placebo. The protective effects of ARALAST NP and GLASSIA were expected to be reflected in the preservation of lung parenchyma, as measured by computerized tomography (CT) lung densitometry. In addition, the functional integrity of lung parenchyma was to be evaluated by measurements of selected respiratory physiology variables.

ARALAST NP and GLASSIA were approved by the Food and Drug Administration (FDA) for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of A1PI. The results of this study, along with available scientific data, may be used to design an adequately powered Stage 2 clinical study.

On 24 JUL 2018, Shire prematurely terminated the entire study following the unanimous vote by the Data Monitoring Committee (DMC) on 25 June 2018. The decision was based on the very low number of randomizations, slow rate of enrolling participants relative to the enrollment targets, and the difficulties of enrolling patients who would have to agree to be potentially randomized to receive placebo. Continuation of the trial would potentially place participants at increased risk due to the study procedures (including but not limited to radiation from the chest CT scan), not receiving active drug and inconvenience of study visits.

This statistical analysis plan (SAP) is based on Protocol Amendment 11 dated 21 JUN 2016 and provides a technical and detailed elaboration of the statistical analyses of efficacy and safety. Shells for tables, figures, and listings are contained in a separate document. Derivations of outcome variables, statistical analyses and summaries detailed in Protocol Amendment 11 which are no longer applicable are not included in this SAP. The summary tables that will be produced are for the disposition, demographic, exposure to investigational product (IP), and overall adverse event (AE) data. The data collected on the electronic case report form (eCRF) will be included in data listings. The listings will include raw (actual) values as recorded on the eCRF. In addition, since no adjudication of the response assessment data will be done, only the data based on the investigators' assessments will be presented in the listings.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To evaluate the effect of weekly A1PI augmentation therapy on the rate of change in lung density assessed by CT lung densitometry, based on pooled data across dose levels for each of the A1PI products.

2.1.2 Secondary Objectives

2.1.2.1 Efficacy

To examine the relationship between A1PI dose (60 mg/kg BW/week and 120 mg/kg BW/week) and the rate of change in lung density assessed by CT densitometry for each of the A1PI products.

2.1.2.2 Safety

- To assess the safety and tolerability of ARALAST NP and GLASSIA augmentation therapy at doses of 60 and 120 mg/kg BW/week.
- To monitor the formation of anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA.

2.1.2.3 Pharmacokinetics

To examine the relationship between A1PI dose and steady-state trough plasma A1PI levels following weekly administration of ARALAST NP or GLASSIA.

2.1.3 Exploratory Objective(s)

[redacted]

[redacted]

2.2 Estimands

A specific description of estimands is not included in the protocol. Given that the study has been terminated early and no efficacy analyses will be provided, estimands have not been further defined for inclusion in this SAP.

2.3 Endpoints

The endpoints provided are from the protocol amendment 11. However, due to the study being prematurely terminated, the derived endpoints will not be presented in the data listing and analysis will not be performed using the endpoints.

2.3.1 Primary Endpoint

Rate of change in lung density (15th percentile of the lung density measurements [PD15] as assessed by CT densitometry), based on Group 1 and Group 2 (ARALAST NP) versus placebo, and Group 3 and Group 4 (GLASSIA) versus placebo

2.3.2 Secondary Endpoint

Rate of change in lung density (as assessed by CT) for each treatment group

2.3.3 Exploratory Endpoints

[redacted]

[redacted]

2.3.4 Safety Endpoints

1. Number and rate of related and unrelated serious and non-serious AEs
2. Number and rate of temporally related serious and non-serious AEs (ie, AEs which began during or within 72 hours following the end of IP infusion)
3. Number and rate of suspected adverse reactions plus adverse reactions
4. Number (proportion) of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped due to AEs
5. Number (proportion) of subjects who develop anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA

2.3.5 Pharmacokinetic Endpoints

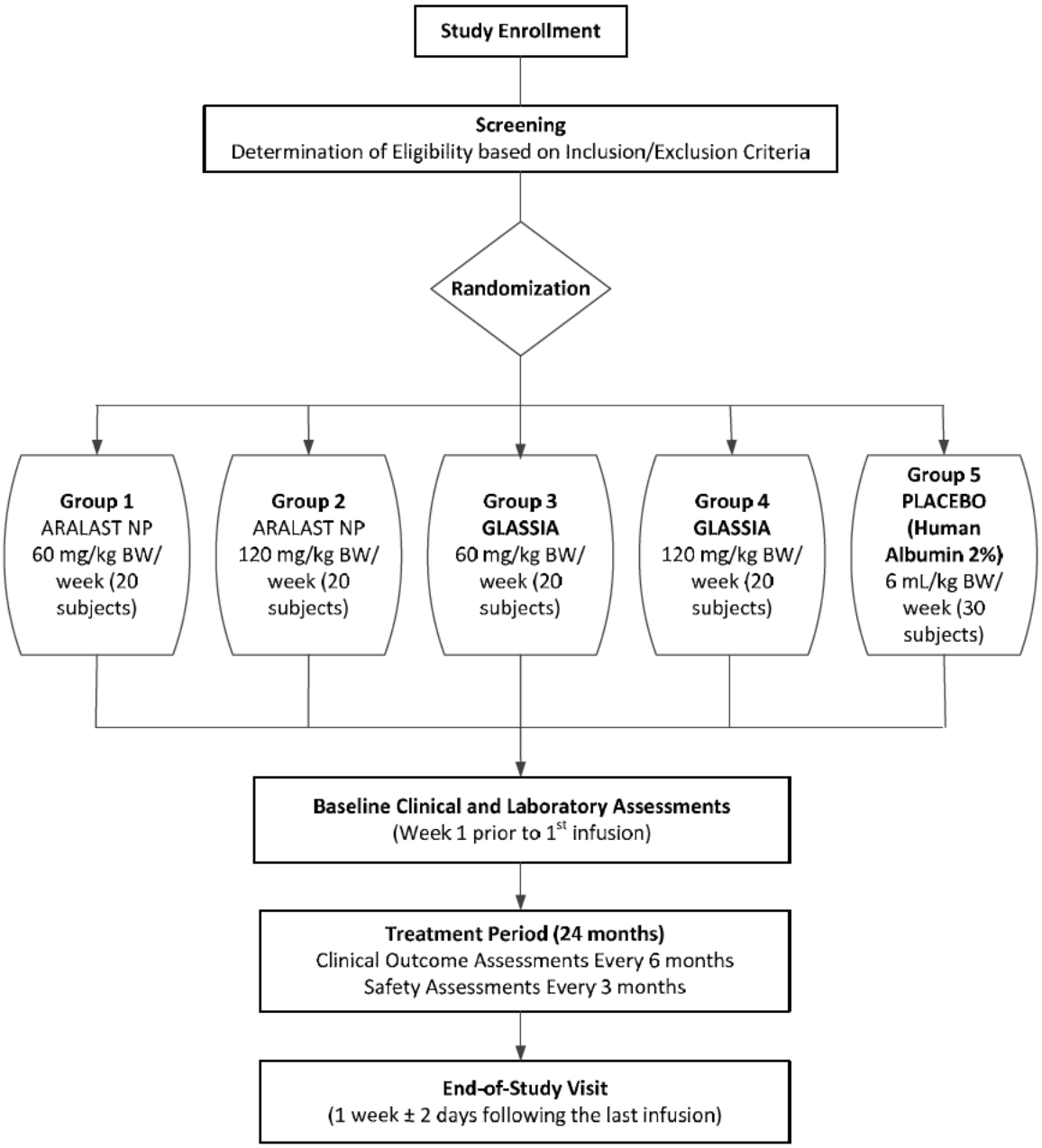
Mean steady state trough concentration of antigenic and functional A1PI for ARALAST NP and GLASSIA at each dose level.

3. STUDY DESIGN

3.1 General Description

This is a Phase 3/4, prospective, randomized, placebo-controlled, double-blind, multicenter pilot study to evaluate the safety and efficacy of weekly administration of ARALAST NP and GLASSIA augmentation therapy in subjects with A1PI deficiency and emphysema/COPD using a dose of 60 mg/kg BW/week (dose currently-approved by the FDA), and a higher, exploratory dose (120 mg/kg BW/week) versus placebo. The flow chart of the study follows:

3.1.1 Figure Study Flow Chart



Approximately 138 adult subjects diagnosed with severe congenital A1PI deficiency and emphysema/COPD were to be enrolled to meet the target of 110 randomized subjects, assuming a 20% screen failure rate. Subjects could be either A1PI naïve (untreated), previously treated, or currently receiving A1PI augmentation therapy at the time of study entry.

Subjects who were receiving or had been treated within 4 weeks of screening, with A1PI augmentation therapy would be required to have their pre-study A1PI augmentation therapy discontinued and undergo a washout period of at least 4 weeks for A1PI levels to return to endogenous (pre-augmentation) levels. Plasma A1PI levels were to be assessed to verify adequacy of A1PI washout and to confirm diagnosis of A1PI deficiency. All other screening procedures were to be performed prior to the completion of the washout period.

Subjects meeting eligibility criteria will undergo baseline assessments prior to the first dose of IP. Subjects were to be randomly assigned to receive one of the five treatments groups for 24 months (104 weeks). The IP was to be administered via weekly IV infusions. The first IP infusion was to be administered at the study site. At the investigator's discretion, subsequent infusions could be administered at the study site or at another suitable location (ie, the subject's home) by a qualified healthcare professional, except for those that occurred during the same week as the clinic visits.

Study visits occurred according to the schedule of events for clinical and laboratory assessments (see Appendix 15). Clinical and/or laboratory assessments, as appropriate, were to be postponed in the event of a moderate or severe lower respiratory tract infection (LRTI)/acute pulmonary exacerbation (APE) until clinical resolution of the LRTI/APE (ie, clinical signs or symptoms were no longer evident) and the subject remained stable for at least 4 weeks (or 90 days in the case of CT assessments) after the end of the LRTI/APE. If a moderate or severe episode of LRTI/APE occurred during the treatment phase, the subject should continue with the planned study visits and receive weekly infusions of IP as planned, unless deemed medically inappropriate by the investigator. All pulmonary exacerbations, AEs, and concomitant medications and/or non-drug therapies were to be recorded during infusion visits. Upon completion of the treatment period, subjects were to be followed for an additional 1 week (± 2 days) for safety monitoring and anti-A1PI antibody assessments.

3.2 Randomization

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized using the interactive voice response system (IVRS)at a ratio of 1:1:1:1:1.5 to receive one of the following five treatments for 24 months (104 weeks):

Group 1: ARALAST NP 60 mg/kg BW/week (20 subjects)
Group 2: ARALAST NP 120 mg/kg BW/week (20 subjects)
Group 3: GLASSIA 60 mg/kg BW/week (20 subjects)
Group 4: GLASSIA 120 mg/kg BW/week (20 subjects)

Group 5: Placebo (Human albumin 2% in normal saline) 6 mL/kg BW/week (30 subjects).

3.3 Blinding

To maintain blinding, all subjects were to receive IP in 2 identical IV bags that were opaque or covered with opaque overwraps. Subjects in Group 1 and Group 3 were to receive 1 IV bag of active IP and 1 IV bag of volume-matched placebo solution (human albumin 2% in normal saline). Subjects in Group 2 and Group 4 were to receive two identical IV bags of active IP. Subjects in Group 5 were to receive two identical IV bags of placebo solution (human albumin 2% in normal saline). Treatment assignment will be blinded to the subject, investigators, study site personnel and the sponsor. Individual study personnel could be unblinded if necessary (e.g. to prepare the infusions or monitor the study source documents).

The randomization assignment is not to be revealed before the study is terminated, except in emergency cases when unblinding is necessary for the clinical management of an SAE. In such events, every attempt must be made to inform the sponsor before breaking the blind or immediately when unblinding has been performed. The investigator may request for the treatment assignment of the specific individual subject involved in the emergency event via the centralized randomization service or the unblinded biostatistician.

3.4 Sample Size and Power Considerations

The sample size proposed for this study will permit estimates of averages and variances in the rate of change of lung density and other parameters after 24 months of treatment in each treatment group and pooled within product. This study will not be powered to permit hypothesis tests of primary or secondary outcome measures.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent.

4.2 Enrolled Set

Enrolled Set consists of all subjects who have signed informed consent and passed inclusion/exclusion criteria.

4.3 Intent-to-Treat Set

Intent-to-Treat (ITT) Set consists of all subjects in the Enrolled Set who have been allocated to a treatment regimen. Analysis will be performed according to allocated treatment regimen regardless of the treatment regimen received.

4.4 Safety Set

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

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all Screen Failures (i.e., subjects who were screened, but not included in the Enrolled Set) will be presented. Any AEs related to Screen Failures will be provided in the AE data listings.

The number of subjects who were included in and excluded from each defined analysis set (i.e., Screened, Enrolled, ITT, and Safety) will be summarized by treatment group, and overall; except for the Screened Set and Enrolled, which will be summarized only overall.

The number and percentage of subjects who completed and prematurely discontinued during the double-blind evaluation phase will be presented for each treatment group and overall for ITT Set. Reasons for premature discontinuation from the double-blind evaluation phase as recorded on the termination page of the electronic Case Report From will be summarized (number and percentage) by treatment group and overall for the Safety Set. All subjects who prematurely discontinued during the double-blind evaluation phase will be listed by discontinuation reason for Enrolled Set.

5.2 Demographic and Other Characteristics at Screening

Descriptive summaries of demographic and characteristics at screening will be presented by treatment group and overall for the Safety Set.

The following demographic characteristics will be summarized in the following order in the tables: age (years), sex, ethnicity, race, weight (kg), height (cm), body mass index (BMI) (kg/m2), and smoking history. Age is calculated as the date of consent minus the

date of birth. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group and overall for continuous variables. The number and proportion of subjects will be presented by treatment group and overall for categorical variables. A listing of the data will be provided using the Safety Set.

5.3 Medical History

Medical history will be collected at the Screening Visit (Visit 1) and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or newer. A listing of the data will be provided using the Safety Set.

5.4 Concomitant Medications, Non-Drug Therapy, and Procedures

Concomitant medications will be coded using the WHO Drug Dictionary dated 01Mar2018. Concomitant non-drug therapies and procedures will be coded using MedDRA Version 21.0 or newer.

All concomitant medications, non-drug therapies, and procedures will be listed for the Safety Set.

5.5 Exposure to Investigational Product

Exposure to IP for the Safety Set will be summarized in terms of number of infusions, duration of exposure, and average weekly dose. The duration of exposure is calculated as the number of days from the date of first dose of IP taken to the date of the last dose of IP taken, inclusively. The average weekly dose is calculated as (total volume administered/ total planned volume) * actual dose (either 60 mg or 120 mg). For placebo, the actual dose would be 0. The average weekly dose is the average of the weekly doses for each subject.

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented to describe the exposure to IP by treatment group and overall.

The number and proportion of subjects with at least one infusion rate change, one infusion rate interruption, or one infusion stopped will be summarized by treatment and overall.

The details of exposure to IP will be listed for the Safety Set.

5.6 Protocol Deviations

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

6. EFFICACY ANALYSES

All raw (actual) efficacy endpoints will be listed for the Safety Set. The efficacy endpoints described in Section 2.3 will not be derived. The following efficacy dataset listings will be presented for lung density CT scan, pulmonary function (spirometry and lung volumes), 6MWT, MMRC dyspnea scale, BODE index, SGRQ-C, and SF-36.

6.1 Analyses of Primary Efficacy Endpoints

The primary efficacy endpoint is rate of change in lung density (15th percentile of the lung density measurements [PD15] as assessed by CT densitometry) that is measured every 6 months. The overall sample size at the termination of the study was small. The analysis and summarization for rate of change in lung density will not be presented.

6.2 Secondary Efficacy Endpoint

Not Applicable

6.3 Multiplicity Adjustment

Not Applicable

6.4 Analyses of Exploratory Endpoint(s)

Not Applicable

6.5 Subgroup Analyses

Not Applicable

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. Safety variables include AEs, clinical laboratory variables, vital signs, and electrocardiogram (ECG) variables.

7.1 Adverse Events

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

An AE (classified by preferred term) that occurs during the double-blind evaluation phase will be considered a treatment-emergent AE (TEAE) if it has a start date on or after the first dose of double-blind IP or if it has a start date before the date of the first dose of double-blind IP, but increases in severity on or after the date of the first dose of double-blind IP.

An overall summary of the number of subjects with TEAEs as well as the number of events by treatment group and overall will be presented. The table will also be summarized by any TEAEs during or within 72 hours following the endo of the IP infusion. The table will include the number and percentage of subjects with any TEAEs, serious TEAEs, severe TEAEs, TEAEs related to IP and TEAEs leading to discontinuation of IP.

All AEs will be listed for the Safety Set.

7.2 Clinical Laboratory Data

Clinical laboratory values will be listed for the Safety Set for the following clinical laboratory variables:

Hematology Hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), leukocytes (ie, white blood cell count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet count.

Biochemistry Sodium, potassium, chloride, bicarbonate, phosphorus, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl-transferase, creatine phosphokinase, bilirubin (direct and total), blood urea nitrogen, uric acid, creatinine, and glucose.

Urinalysis Color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate, leukocyte esterase, and microscopic examination (red blood cell, white blood cell, bacteria, casts). Only recorded at screening.

Other Cotinine and pregnancy test.

7.3 Vital Signs

All vital signs data (e.g., systolic and diastolic blood pressure, pulse rate, respiratory rate, body weight, body temperature, and BMI) will be listed for the Safety Set.

7.4 Electrocardiogram (ECG)

All ECG data (e.g., heart rate, PR interval, QRS interval, QT interval, and QTc interval) will be listed for the Safety Set.

7.5 Other Safety Data

If available, the number of subjects with anti-A1PI antibodies will be summarized by treatment group and overall over the schedule time point of collections. The immunogenicity data will be listed for the Safety Set.

8. PHARMACOKINETIC ANALYSIS

8.1 Drug Concentration

All antigenic and functional A1PI levels will be listed for the Safety Set.

9. DATA MONITORING COMMITTEE

This study was monitored by a DMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC was composed of recognized experts in the field of alpha1-proteinase inhibitor deficiency and COPD clinical care and research who were not actively recruiting subjects.

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

10. DATA HANDLING CONVENTIONS

10.1 General Data Reporting Conventions

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

Refer to the Shire TFL Standards for rules on the number of decimal places to present.

10.2 Definition of Baseline

Not Applicable

10.3 Definition of Visit Windows

Not Applicable

10.4 Derived Efficacy Endpoints

Not Applicable

10.5 Repeated or Unscheduled Assessments of Safety Parameters

Not Applicable

10.6 Handling of Missing, Unused, and Spurious Data

10.6.1 Missing Date of Investigational Product

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

10.6.2 Missing Date Information for Concomitant Medications, Non-Drug Therapies, and Procedures

The missing dates for concomitant medications, non-drug therapies, and procedures will not be imputed. The dates will be presented “as is” in the data listings.

10.6.3 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g.

AE start year and month are the same as the year and month of the first dose of IP, then the AE will be classified as treatment-emergent.

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

10.6.3.1 Incomplete Start Date

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

10.6.3.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields.

10.6.3.1.2 Missing Month Only

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

10.6.3.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day
- If either the year is before the year of the date of the first dose of IP or if both years are the same, but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of IP or if both years are the same, but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

10.6.3.2 Incomplete Stop Date

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

10.6.3.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields.

10.6.3.2.2 Missing Month Only

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

10.6.3.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day
- If either the year is before the year of the date of the last dose of IP or if both years are the same, but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of IP or if both years are the same, but the month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day.

10.6.4 Character Values of Clinical Laboratory Variables

The character values of the clinical laboratory variables will be presented “as is” in the data listings.

11. ANALYSIS SOFTWARE

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

12. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

As indicated in Section 1, Shire prematurely terminated the entire study on 24 July 2018 following the unanimous vote by the DMC on 25 June 2018. The decision was based on the very low number of randomizations, slow rate of enrolling participants relative to the enrollment targets, and the difficulties of enrolling patient who would have to agree to be potentially randomized to receive placebo. Continuation of the trial would potentially place participants at increased risk due to the study procedures (including but not limited to radiation from the chest CT scan), not receiving active drug and inconvenience of study visits.

This SAP includes the analyses that will be provided for the abbreviated study report. The derivations, statistical analyses and summaries of the study endpoints (See Section 2.3) noted in Protocol Amendment 11 are no longer applicable. The only summary tables that will be produced are for the disposition, demographic, exposure to IP, and overall AE data. A full set of data listings will be produced. The listings will include raw (actual) values. In addition, since no adjudication of the response assessment data will be done, only the data based on the investigators' assessments will be presented in the listings. The Full Analysis, Modified Full Analysis, and Per-Protocol Sets will not be defined because the populations will not be needed to list the data. The listings will be presented for the largest meaningful analysis set (e.g., Enrolled Set or Safety Set), depending on the content.

13. REFERENCES

Not Applicable

14. APPENDICES

14.1 Schedule of Study Procedures and Assessments

Table 14-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment		Treatment Period										Study Completion	Early Termination
	Scr (Max 6 Weeks)	Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Informed Consent[a]	X												
Eligibility Determination	X												
Demographics	X												
Medical, Medication, and Non-Drug Therapy History	X												
Smoking history	X												
Body Height	X												
Body Weight[b]	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
BMI	X	X			X		X		X		X		X[c]
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X[e]										X		
Chest X-Ray/CT	X												
Pulmonary function tests[f]	X	X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
Lung density CT scan[i]		X[g,h]			X[g,i]		X[g,i]		X[g,i]		X[g,i]		X[c]

Table 14-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment		Treatment Period										Study Completion	Early Termination
	Scr (Max 6 Weeks)	Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
6MWT		X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
MMRC dyspnea scale		X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
BODE Index		X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
HRQoL (SGRQ-C and SF-36)		X[g,h]			X		X		X		X		X[c]
Clinical Laboratory Assessments[j]	X	X[g,h]	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
COPD Exacerbations	X	Weekly (Weeks 1 – 104)										X	X
IP Treatment[k]		Weekly (Weeks 1 – 104)											
Telephone follow-up[l]		Weekly (Weeks 1 – 104)											
Concomitant Medications and non-drug therapies	X	Weekly (Weeks 1 – 104)										X	X
Adverse Events	X	Weekly (Weeks 1 – 104)										X	X

Abbreviations: Scr = Screening; BMI = Body mass index; ECG = Electrocardiogram; CT = Computed tomography; 6MWT = 6-minute walk test; MMRC = Modified Medical Research Council; BODE = Body mass index, airflow obstruction, dyspnea, and exercise capacity index; HRQoL = Health-related quality of life; SGRQ-C = St. George respiratory questionnaire for chronic obstructive pulmonary disease (COPD) patients; IP = Investigational product.

[a] Written informed consent must be obtained prior to any study procedures including screening.
[b] The subject's body weight measured at each office visit will be used to calculate the infusion volume (mL) for IP administration. Adjustment based on body weight changes during the course of the study may be made if necessary.
[c] To be performed only if the last assessment is performed more than 13 weeks prior to the early termination visit.
[d] Vital signs including body temperature, heart rate, blood pressure, and respiratory rate will be measured at screening, during each infusion visit (within 60 minutes prior to the start of an IP infusion and within 60 minutes after the end of an IP infusion), and at the study completion/early termination visit. Vital signs will be measured when subjects are in the sitting position after a 5-minute rest.
[e] 12-Lead ECG previously obtained within 26 weeks prior to screening may be used, if available.
[f] Pulmonary function tests include spirometry (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]), single-breath diffusing capacity of carbon monoxide (DL_{CO}), and lung volume measurements (total lung capacity [TLC], functional residual capacity [FRC], residual volume [RV], and inspiratory capacity [IC]). Spirometry is to be performed before and at 30 (± 5) minutes following inhalations of a short-acting inhaled bronchodilator (eg, salbutamol bromide at a total dose of 400 μg [2 x 200 μg or 4 x 100μg puffs] or its equivalent). Measurements of diffusing capacity and lung volumes are to be performed prior to bronchodilator administration and spirometry.
[g] To be performed prior to IP administration.
[h] Values obtained prior to initiation of IP treatment during Week 1 visit will serve as the baseline values.
[i] Subjects must have met all eligibility criteria prior to undergoing the baseline CT scans of the lungs (Week 1 prior to IP infusion). Subsequently, subjects will undergo CT assessment every 26 weeks (± 1 week) or early termination visit. See the CT lung densitometry acquisition and analysis manual for further details.
[j] For laboratory assessments, see Table 14-2.
[k] The first IP infusion must take place at the study site. At the investigator's discretion, subsequent infusions may be administered at the study site or at another suitable location by a qualified healthcare professional, except for those that occur in the same week as the clinic visits during Weeks 4, 13, 26, 39, 52, 65, 78, 91, and 104 described in the table above.
[l] Following each infusion visit, telephone follow-up will be conducted by the investigator/designee at 72 hours (+ 1 business day) to document AEs, and/or administration of concomitant medications or non-drug therapies, which may have occurred within 72 hours after the completion of an infusion. Any adverse events that occur and/or concomitant medications/non-drug therapies that the subject takes after the post-infusion telephone follow-up will be collected during the subsequent weekly infusion visit.

14.2 Clinical Laboratory Assessment

Table 14-2
Clinical Laboratory Assessments

Procedure/ Assessment	Scr (Max 6 Weeks)	Treatment Period										Study Completion	Early Termination
		Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Hematology[a]	X	X[b,c]	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[d]	X	X[b,c]	X	X	X	X	X	X	X	X	X	X	X
Serum IgA	X												
Viral Serology[e]	X											X	X
Cotinine	X	X		X	X	X	X	X	X	X	X		X
Plasma A1PI (antigenic)	X	X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Plasma A1PI (functional)		X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Anti-A1PI Binding Antibodies		X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Anti-A1PI Neutralizing Antibodies		X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
[redacted]													
Urinalysis[f]	X												
Pregnancy Test[g]	X											X	X

Abbreviations: Scr = Screening; IgA = Immunoglobulin A; A1PI = Alpha1-proteinase inhibitor.

[a] Hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), leukocytes (ie, white blood cell count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet count.

[b] To be collected within 4 hours prior to the start of the IP infusion on the day of an infusion visit. Note that neutralizing antibodies will only be assayed in the case that a positive binding antibody response is recorded for the subject

[c] Values obtained prior to initiation of IP treatment during Week 1 visit will serve as the baseline values.

[d] Clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, phosphorus, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl-transferase, creatine phosphokinase, bilirubin (direct and total), blood urea nitrogen, uric acid, creatinine, and glucose.

[e] Viral serology includes hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency type 1/2 antibody screens, as well as parvovirus 19 serology and nucleic acid test.

[f] Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

[g] For women of childbearing potential only.