Statistical Analysis Plan

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Study Name	ADVM-043-01
Study Title	Phase 1/2 Study of Intravenous or Intrapleural Administration of a Serotype rh.10 Replication Deficient Adeno-associated Virus Gene Transfer Vector Expressing the Human Alpha-1 Antitrypsin cDNA to Individuals with Alpha-1 Antitrypsin Deficiency (ADVANCE)
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List of Abbreviations

ADVM-043	AAVrh.10 vector expressing human A1AT
AE	adverse event
AST	aspartate aminotransferase
BAL	bronchial alveolar lavage
CBC	complete blood count
BEVS	baculovirus expressions vector system
cDNA	complementary DNA
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
COPD	chronic obstructive pulmonary disease
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ELF	epithelial lining fluid
ELISA	enzyme-linked immunosorbent assay
EOS	end-of-study visit
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEF	isoelectric focusing
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	institutional review board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NE	neutrophil elastase
NOAEL	no-observed-adverse-effect level
PAT	protein augmentation therapy
PBMC	peripheral blood mononuclear cell
PE	physical examination
[redacted]	[redacted]
PI	Principal Investigator
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TLC	total lung capacity
ULN	upper limit of normal
vg	vector genomes
WBC	white blood cell

1. Revision History

Version Number	Version Date	Author	Description of Significant Changes from Previous Approved Version
4.0	04-Sep-2019	[redacted]	Updated to reflect [redacted] and updates from Amendment 7. None of the previous versions were finalized.

2. Introduction

Study ADVM-043-01 is a Phase 1/2 study being conducted to test the safety and efficacy of ADVM-043 in subjects with alpha-1 antitrypsin (A1AT) deficiency. These subjects possess a mutation in the human A1AT gene that affects the production and normal functioning of A1AT protein. A1AT has been found to be most active in the lung, where it balances the activity of neutrophil elastase, an enzyme released in the setting of inflammation or infection. Unchecked enzymatic activity can lead to destruction of lung tissue and insufficient anti-neutrophil elastase activity, resulting in early-onset emphysema. A1AT deficiency resulting in 5-fold or greater decreases in plasma A1AT levels is associated with a greater risk for developing emphysema, chronic obstructive pulmonary disease (COPD), bronchiectasis, and asthma.

ADVM-043 will be administered by 2 routes: in Part A, a single dose in each of 4 cohorts will be administered by intravenous (IV) infusion. Based on the safety and efficacy data from Part A, the study may proceed to Part B. In part B of the study, ADVM-043 will be administered by intrapleural injection. The successful completion of this study will provide critical safety and preliminary efficacy data to determine whether to proceed to a Phase 3 pivotal study.

This statistical analysis plan (SAP) is based on the clinical study protocol ADVM-043-01 Protocol Amendment 7 dated 30 October 2018 and its associated electronic case report forms (eCRFs). This document describes the rules to be used in the analysis and representation of safety and efficacy data as presented in the clinical protocol.

3. Objectives

3.1. Primary Objectives

- *To assess the safety of ADVM-043 following IV administration*

3.2. Secondary Objectives

- *To assess the effect of ADVM-043 on plasma A1AT concentrations following IV administration [up to 52 weeks]*
- *To assess the safety and effect of ADVM-043 following intrapleural administration**

**Safety and efficacy data, including maximum tolerated dose (MTD), from Part A will be considered when determining whether to proceed to Part B.*

Based on the safety and efficacy data from Part A, and in consultation with the Study Principal Investigators, the study did not proceed to Part B and will be excluded from all the analyses.

4. Investigational Plan

4.1. Overall Study Design and Plan

Study ADVM-043-01 is a Phase 1/2, open-label, multicenter, dose-escalation, first-in-human study to evaluate the safety and efficacy of ADVM-043 (AAVrh.10 vector expressing human A1AT), an investigational medicinal product (IMP) that is intended to deliver a functional gene to the liver of the subjects with A1AT deficiency.

The study is intended to test the hypothesis that ADVM-043 to individuals with A1AT deficiency is safe and results in persistent potentially therapeutic levels of A1AT in blood and alveolar epithelial-lining fluid (ELF). Subjects enrolled in the study will be treatment-naïve to protein augmentation therapy (PAT) or will have stopped receiving PAT at least 8 weeks prior to treatment administration. Therefore, detection of plasma A1AT levels over baseline will provide evidence of activity of ADVM-043.

In Part A of the study, ADVM-043 will be administered by IV infusion up to 4 dose-level cohorts. In each cohort, ADVM-043 will be initially administered to 2 subjects and may be administered to an additional 3 subjects in each cohort level after review by a data monitoring committee (DMC). Safety and efficacy data, including the maximum tolerated dose (MTD) observed from Part A, will be considered when determining whether to proceed to Part B and at what dose level.

In Part A, the first subject assigned to a cohort will receive a single IV infusion of ADVM-043 at 8×10^{13} vg. Beginning on the day of treatment (Day 0), the subject will be monitored for safety and treatment effects at protocol-specified study visits (Appendix 13.1). The first subject will be considered a sentinel subject and a minimum of 2 weeks (14 days) will separate dosing of the first and second subjects within a cohort. There will be a minimum of 4 weeks between dosing of the last subject in one cohort and the first subject in the next cohort which will include a DMC review of the safety and efficacy data within a dosing cohort.

In Part B of the study, ADVM-043 will be administered by intrapleural injection at 1 dose-level. The Schedule of Assessments is in Appendix 13.1.

4.2. Study Endpoints

4.2.1 Safety Endpoints

Type, frequency, severity, duration, and relationship to study drug of any AEs and laboratory abnormalities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.2.2 Efficacy Endpoints

- *Changes in plasma concentrations of M-specific A1AT [up to 52 weeks]*
- *Changes in total plasma concentrations of A1AT [up to 52 weeks]*

[redacted]

Based on the safety and efficacy data from Part A, and in consultation with the Study Principal Investigators, the study did not proceed to Part B and will be excluded from all the analyses.

4.3. Definition of Dose limiting toxicity

The first subject dosed will be considered the sentinel subject. The proposed dosing interval is at least 14 days between the first (sentinel) subject and the second subject dosed within a cohort provided there are no safety concerns in the sentinel subject.
A dose-limiting toxicity (DLT) is defined as any AE with severity Grade ⩾3 attributed to ADVM-043 and that occurs within the DLT observation period. The DLT observation period is based on data from ongoing studies in liver-targeting gene therapy showing that treatment-related AEs have occurred in general within 4 weeks of study treatment and have not led to long term sequelae.

The DLT observation period for the sentinel subject will be 6 weeks (14 days plus 4 weeks) post-study treatment and for the second or any subsequent subject within the same dosing cohort, 4 weeks post-study treatment. The DLT observation period will occur during the DMC and Adverum's review

period, during which decisions will be made to dose escalate to the next cohort, or to further expand an ongoing dose cohort.

Within each dosing cohort, the first DLT will result in cohort expansion from a total of 2 subjects to a total of 5 subjects. If more than one DLT occurs within the same dose cohort, the maximum tolerated dose (MTD) will have been exceeded; de-escalation and cohort expansion of the prior cohort or an additional intermediate dose may be considered. The MTD will be the dose at which no more than 1 of the 5 subjects in an expanded cohort experiences a DLT.

If no DLTs are observed within the 2 subjects dosed, dose-escalation can proceed, and the Sponsor may also elect to expand the cohort to further evaluate safety or efficacy endpoints.

If only 1 DLT occurs in a total of 5 subjects within a dosing cohort, the DMC and the Sponsor will review all safety data and recommend dose-escalation or progression to Part B.

Enrollment will be suspended pending adjudication by the DMC if, at any time during the study, any of the following occur:

- *Any Grade 4 or 5 AE, regardless of attribution*
- *Any Grade 3 AE attributed to ADVM-043*
- *Evidence of acute liver injury (ALT >5 × ULN)*

5. General Statistical Considerations

The study is a Phase 1/2 safety and preliminary measure of efficacy study. As a Phase 1 safety study, no formal statistical analysis is required. Descriptive and exploratory analyses will be performed on all data collected in this study to gain further insight into the efficacy and safety of this gene transfer therapy.

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. All data will be provided in by-subject data listings.

Decimal rules for categorical summaries:

When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that cohort within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to one decimal place, except 100%, which will be displayed without any decimal places.

Decimal rules for continuous summaries:

- If the original value has decimal places 2 or less: mean and median will have one additional decimal place and SD will have 2 additional decimal places

- If the original value has 3 or more decimal places: mean, median and SD will all have 3 decimal places

Minimum and maximum will always have the same decimal places as the original measure, up to a maximum of 3 decimal places.

5.1. Sample Size

Formal sample size calculations were not performed. The total number will range between 2 and 25 subjects with 2-5 subjects per cohort. The initial cohort size of 2 was chosen because:

- It minimizes the number of subjects potentially exposed to a sub-therapeutic dose of ADVM-043, which has limited potential for a second administration due to the development of neutralizing antibodies.

- A1AT deficiency is a rare disease (prevalence of approximately 1 to 5 per 10,000); this small number of potential subjects will further be limited by the protocol exclusion criteria such as the presence of pre-existing neutralizing antibodies to AAVrh.10 and the requirement for the 8-week washout period for subjects on PAT before treatment with ADVM-043.

- Data from historical clinical trials show a low rate of withdrawal which further supports the initial cohort size of 2 because the likelihood of incomplete data is predicted to be low.

If a subject withdraws prior to completion of the DLT observation window, the subject will be replaced and followed for DLTs before decisions regarding cohort expansion are made.

5.2. Randomization, Stratification, and Blinding

This is an open-label study, so randomization and blinding are not applicable.

5.3. Analysis Set

Enrolled set will consist of all subjects who were dosed.

The full analysis set (FAS) will consist of all subjects who receive any amount of ADVM-043.

The FAS will be used for presenting demographics, baseline characteristics, efficacy, and overall safety and tolerability assessments. Assessments will be presented by cohorts and total.

5.4. Analysis Variables

All the data conventions below are applicable only for summaries. Listings will be as reported in CRF unless stated otherwise.

5.4.1. Study Visit and Window

Screening procedures are to be completed a maximum of 3 months prior to ADVM-043 administration (Day 0). Screening assessments may be performed on multiple days. Subjects may be re-screened upon consultation with Adverum. The Screening visit is defined as ≤3 Month before Day 0. The Baseline visit is defined as prior to study treatment (within 36 hours of study administration) on Day 0. (Schedule of Assessments is in Appendix 13.1).

5.4.2. Data Handling

All available efficacy and safety data will be included in data listings and tabulations as stated in section 6.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

5.4.3. Protocol deviations

A significant deviation is defined as a protocol deviation that affects primary efficacy assessments, the safety of a subject or the scientific value of the trial ('Study Deviation Manual'). Significant deviations can include nonadherence to entry criteria; enrollment of the subject without prior Sponsor approval; or nonadherence to FDA regulations or ICH GCP guidelines. Protocol deviations will be reviewed prior to database lock to determine if significant, and all significant deviations will be flagged.

5.4.4. Age

Age will be derived as follows:

Age (in years) = (Informed Consent date – Birthdate)/365.25

5.4.5. Medication flags

If a medication started and ended before Day 0 ([redacted] as directed by protocol) then, it is considered as prior medication;

If the start date is missing and the end date is before Day 0 then, it is prior medication;

If the start date is before Day 0 and the end date is on Day 0 then, it is prior medication;

If the start date is before Day 0 and the end date is after Day 0 then, it is concomitant medication;

If the start date is before Day 0 and the end date is missing then, it is concomitant medication;

If both the start and end dates are missing then, it is concomitant medication;

If the start date is missing and end date is after Day 0 then, it is concomitant medication;

If both start and end dates are on or after Day 0 then, it is concomitant medication;

Medications for which missing start and/or stop dates make it impossible to determine the prior or concomitant status, will be classified as concomitant medications;

[redacted] concomitant medication, which are to be started on Day -1 prior to administration of ADVM-043.

5.4.6. DLCO Calculation

The DLCO data are collected at the local lab for each site, so results may be collected in domestic or SI units. The DLCO results in domestic units (mL/min/mmHg) will be converted to SI units (mmol/min/kPa) prior to analysis using the following conversion factor:

DLCO in SI units = (DLCO in domestic units) / 2.986

5.4.7. Adverse Event Flags

TEAE Flag: A treatment-emergent adverse event (TEAE) is any event that was not present before exposure to the IMP or any event already present that worsens in either intensity or frequency after exposure to the IMP. All AEs that started on/after Day 0 will be flagged as 'TEAE'.

DLT Flag: A dose-limiting toxicity (DLT) is defined as any AE Grade ≥3 attributed to ADVM-043 and occurring within the DLT observation period. The DLT observation period for the sentinel subject is 6 weeks (14 days plus 4 weeks) post study treatment; and for the second or any subsequent subject within the same dosing cohort, 4 weeks post study treatment. This takes into consideration the 14-day minimum interval between the sentinel subject and the second subject dosed in a cohort and the 4-week DLT observation period.

Related AEs Flag: AEs that are possibly, probably and definitely related to study treatment will be flagged as 'related' AEs. TEAEs with missing relationship will be considered as a related event. Relationship to ADVM-043 and Prednisone will be flagged separately.

Severity Flag: Subjects with the same TEAE and different severities will be flagged for the most intense severity. i.e., If the same event has been reported twice with severity 'Grade 1 – Mild' and 'Grade 3 – Severe' then the subject will be flagged as 'Grade 3 – Severe'. TEAEs that are missing severity will be presented in summary tables as 'Grade 3 – Severe'.

5.4.8. Duration of AEs

Duration of Adverse events (days) will be calculated as follows: (Event End date – Event Start date) + 1.

For the events that are ongoing at end of study, date of end of study will be considered as Event End date.

5.4.9. Laboratory Abnormalities

The standard laboratory results will be compared against the standard low/high ranges reported.

If result < the low range, then, the result will be flagged as 'Low'. If the result is > the high range then, the result will be flagged as 'High'. Otherwise, the result is between the low and high ranges and will be flagged as 'Normal'.

Minimum and Maximum post-baseline abnormalities will also be flagged for each subject.

For urinalysis parameters, the results will be categorized as 'Normal' and 'Abnormal'.

5.4.10. PCS Abnormalities Criteria: ECG

The criteria for potentially clinically significant (PCS) abnormalities are shown in the following table:

ECG: Criteria for PCS Abnormalities
Ventricular Rate (Beats/Min) • <45 • >100
P-R Interval (msec) • <100 • >200
QRS Duration (msec) • < 80 • > 200
Q-T Interval (msec) • <250 • >500
Q-Tc Interval (msec) • <250 • >500

5.4.11. PCS Abnormalities Criteria: Vital Signs

The criteria for clinically relevant vital signs abnormalities are shown in the following table:

Vital Signs: Criteria for PCS Abnormalities
Systolic Blood Pressure • <90 mmHg • >180 mmHg
Diastolic Blood Pressure • <50 mmHg • >100 mmHg
Temperature • <36 ^{0} C • >38 ^{0} C
Heart Rate • <40 beats per minute • > 100 beats per minute
Respiratory Rate • <12 breaths per minute • >20 breaths per minute

5.4.12. Protein Augmentation Therapy (PAT) at baseline

PAT use at baseline (washout of at least 8 weeks from last PAT dose and baseline) will be flagged as below.

- Subjects with prior use of PAT at baseline
- Subjects without prior use of PAT at baseline

The following medications are considered Protein Augmentation Therapy (PAT) with trade names Glassia, Prolastin-C, Aralast NP or Zemaira and generic name: Alpha1-proteinase Inhibitor (human).

5.4.13. [redacted] A1AT Data

[redacted]

Result derivations:

- If the result for an individual pool is [redacted], then it is considered as a positive result.
- Cumulative result is calculated by subtracting the medium control individually from the positive samples and then by adding only the positive responses.

6. Statistical Analyses

All summaries will be presented by cohorts and total. All summaries will be presented for FAS population.

All data listings will be presented as collected in CRF. All listings will be based on FAS population, unless specified.

Based on the safety and efficacy data from Part A, and in consultation with the Study Principal Investigators, the study did not proceed to Part B and will be excluded from all the analyses.
IV Cohort 4 was not enrolled due to sponsor's decision and will be excluded from all the analyses.

6.1. Subject Disposition

A summary of disposition of subjects will include the number and percentage of subjects for the following categories but not limited to: subjects screened, subjects treated (FAS population), subjects completing DLT observation period and completing the study, discontinued from the study and primary reason for discontinuation.

The reasons for subjects not completing the study include:

- Lost to follow-up
- Withdrawal of consent for participation in the study
- Adverse event(s) that put the safety of the subject at risk

- Major protocol deviation prior to treatment. The Investigator should discuss the protocol deviation with the Medical Monitor before withdrawing the subject
- Investigator decides to discontinue the subject
- Sponsor decides to discontinue the subject.
- Other

Subject disposition information will be listed by dose cohort and subjects.

A summary of screen failures includes subjects who failed to meet eligibility criteria at screening and baseline visits with corresponding reasons for screen failure. Any discontinuation/withdrawal prior to dosing is considered a screen failure. Percentages will be based on all subjects screened.

Inclusion / Exclusion criteria will be listed for all subjects screened.

In Mock Shell: Table 14.1.1.1, Table 14.1.1.2, Listing 16.2.1 and Listing 16.2.3.4

6.2. Significant Protocol Deviations

A summary of significant protocol deviations will include number and percentage of subjects with any significant protocol deviation along with their categories.

All protocol deviations reported will be listed by dose cohort and subjects. All the significant protocol deviations will be listed separately along with their impact on the analysis and corresponding mitigation action items.

In Mock Shell: Table 14.1.2, Listing 16.2.2.1 and Listing 16.2.2.2

6.3. Demographics and Baseline characteristics

A summary of demographic and baseline characteristics will include the following parameters:

- Age
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Subject demographics information will be listed by dose cohort and subject.

In Mock Shell: Table 14.1.3 and Listing 16.2.3.1

6.4. Disease Characteristics

A summary of disease characteristics at baseline will include the following parameters:

- A1AT genotype
- Prior use of Protein Augmentation therapy*
- [redacted]

*The following medications are considered Protein Augmentation Therapy (PAT) with trade names Glassia, Prolastin-C, Aralast NP or Zemaira and generic name: Alpha1-proteinase Inhibitor (human).

A1AT genotype results collected at screening will also be listed by dose cohort and subject.

In Mock Shell: Table 14.1.4 and Listing 16.2.3.2

6.5. Medical History

A summary of medical history will include number and percentage of subjects with any medical history. This summary will also include number and percentage of subjects with medical history by system organ class and preferred term.

All medical history information will be listed by dose cohort and subject.

In Mock Shell: Table 14.1.5 and Listing 16.2.3.3

6.6. Other Screening data

Chest X-Ray results and Hepatic Ultrasound Observations Results collected at screening will be listed by dose group and subject.

In Mock Shell: Listing 16.2.8.9 and Listing 16.2.8.10

6.7. Prior and Concomitant medication

Concomitant medications include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications used between signing the informed consent form (ICF) and the End-of-Study Visit (EOS).

Verbatim terms for prior and concomitant medications are to be coded using the World Health Organization Drug Dictionary (September 2017).

A summary of prior/concomitant medications will include number and percentage of subjects with any prior/concomitant medication and the total number of prior/concomitant medications. This summary will also include number and percentage of subjects with the corresponding medication by Therapeutic Main group (ATC Level 2) and preferred term.

Prior and concomitant medications will be presented separately.

Prohibited concomitant medications include protein augmentation therapy (PAT) for the treatment of alpha-1 antitrypsin deficiency for 3 months following treatment with IMP (Day 0) or other investigational therapies.

After the Week 12 visit, the treating physician in consultation with the Medical Monitor may decide to resume or start PAT, based on clinical judgment as well as data from study participation. Subjects who resume or start PAT post-treatment will remain in the study and continue to be followed for safety related parameters according to the schedule of assessments.

All prior and concomitant medications will be listed by dose cohort and subject. Prohibited medications will be flagged in the listings.

In Mock Shell: Table 15.1.6 and Listing 16.2.4.1

6.8. Study Treatments

ADVM-043 is a genetically engineered, replication-incompetent, adeno-associated viral vector of serotype rh.10 (AAVrh.10), encoding human alpha-1 antitrypsin (A1AT complementary deoxyribonucleic acid (cDNA). Once thawed, ADVM-043 is a clear, colorless liquid.

In Part A of the study, ADVM-043 will be administered by IV up to 4 dose-levels.

- Cohort 1 ADVM-043 at 8×10^{13} vg
- Cohort 2 ADVM-043 at 4×10^{14} vg
- Cohort 3 ADVM-043 at 1.2×10^{15} vg
- Cohort 4 ADVM-043 at 4.8×10^{15} vg

Part B of the study was not continued and will be excluded from this analysis plan.

No subjects were enrolled into Cohort 4 of the study.

ADVM-043 exposure details will be listed by dose cohort and subject.

In Mock Shell: Listing 16.2.5

6.9. Efficacy Analysis

[redacted] All efficacy analysis will be based on FAS population.

6.9.1. Efficacy Endpoints

A descriptive summary of each of the below efficacy endpoints will be presented for actual results as well as change from baseline.

- Concentrations of total and M-specific A1AT over time

[redacted]

[redacted]

6.9.3. Biomarker Figures

Only the cumulative of positive pools (subtracting the medium) as mentioned in section 5.4.13 will be plotted for [redacted] data in all figures below.

Bar Plot:

- Plasma Concentration of total A1AT will be plotted by week and subject to visualize the trend over weeks. X-axis will be week and Y-axis will be the total A1AT plasma concentration. Each bar represents a subject within each cohort. Each cohort will be presented in a separate figure.
- The same will be repeated for M-specific Plasma Concentration of A1AT.

[redacted]

Line Plot:

- Plasma Concentration of M-specific A1AT and ALT will be plotted together to visualize the change in M-specific A1AT along with ALT for each subject. X-axis will be week and Y-axis will be the M-specific A1AT plasma concentration for the bars and ALT for the line. Upper limit of Normal for ALT will also be presented as a reference line. Each subject will be presented in a separate figure.
- The same will be repeated for M-specific A1AT and [redacted]. X-axis will be week and Y-axis will be the M-specific A1AT plasma concentration for the bars and [redacted] for the line. Each subject will be presented in a separate figure.
- The same will be repeated for M-specific A1AT [redacted] value. X-axis will be week and Y-axis will be the M-specific A1AT plasma concentration for the bars [redacted]. Each subject will be presented in a separate figure.

In Mock Shell: Figure 14.2.5.1, Figure 14.2.5.2, Figure 14.2.5.3, Figure 14.2.5.4, Figure 14.2.5.5, Figure 14.2.5.6 and Figure 14.2.6.1.

6.10. Safety Analysis

The safety and tolerability of ADVM-043 are to be assessed by determining the frequency and percentages, severity, and relationship to study drug of AEs; and changes in the laboratory and other safety parameters (e.g., vital signs, ECG, etc.) by cohort. In addition, safety assessments will include urine pregnancy testing for women of childbearing potential. All safety data will be listed and summarized by cohort using the FAS population.

6.10.1. Adverse Events

An AE is any untoward medical occurrence in an enrolled subject regardless of its causal relationship to the IMP. A treatment-emergent adverse event (TEAE) is any event that does not present before exposure to the IMP or any event already present that worsens in either intensity or frequency after exposure to the IMP.

A summary of TEAEs will include numbers and percentages of subjects with TEAE, DLT, ADVM-043-related TEAE, Prednisone-related TEAE, TEAE ≥ grade 3, serious TEAE, treatment-related serious TEAE and Fatal TEAE.

AEs are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 20.1) classification to give a preferred term (PT) and system organ class (SOC) for each event.

In Mock Shell: Table 14.3.1.1

6.10.1.1. Incidence of Treatment Emergent Adverse Events

Numbers and percentages of subjects with TEAEs will be presented. Summary of TEAEs will be presented by SOC and PT. These tables are to include overall totals for AEs within each organ class.

The incidence of TEAEs table will include only one occurrence of a preferred term (PT) per subject. If a subject report the same PT multiple times, then that the subject will be counted once under the

PT. If a subject report multiple TEAEs within the same SOC, then the subject will be counted once under that corresponding SOC.

The incidence of DLT will also be summarized by dose cohort and total in a similar manner.

Treatment related TEAEs will also be summarized by dose cohort and total as mentioned above. All AEs that are possibly, probably and definitely related to study treatment will be considered as treatment related TEAEs. Relationship to ADVM-043 and Prednisone will be presented separately.

All Adverse events will be listed by dose cohort and subject and TEAEs will be highlighted. All DLTs, Serious TEAEs and TEAEs leading to study discontinuation will also be listed individually.

Duration of AEs will be presented in the listing.

In Mock Shell: Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.4, Table 14.3.1.5, Listing 16.2.7.1, Listing 16.2.7.2 and Listing 16.2.7.3

6.10.1.2. Severity of Adverse Events

The intensity of the AE will be rated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A summary of TEAEs by severity and dose cohort will be presented. If a subject reported multiple occurrence of the same TEAE, only the most severe occurrence will be presented.

In Mock Shell: Table 14.3.2.1

6.10.1.3. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence in an enrolled subject, regardless of its causal relationship to the IMP that results in death, is immediately life-threatening, requires in subject hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Important medical events that may not meet these criteria may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Numbers and percentages of subjects with SAEs will be presented. Summary of SAEs will be presented by SOC and PT. These tables are to include overall totals for AEs within each organ class.

The incidence of SAEs table will include only one occurrence of a preferred term (PT) per subject. If a subject report the same PT multiple times, then that the subject will be counted once under the PT. If a subject report multiple SAEs within the same SOC, then the subject will be counted once under that corresponding SOC.

ADVM-043 related SAEs will also be presented in a similar manner.

In Mock Shell: Table 14.3.2.2 and Table 14.3.2.3

6.10.1.4. Death

Any death during this trial will be collected and presented in a listing.

The information that is presented will include date of death, PT, and days on trial since the treatment administration on Study day 0.

In Mock Shell: Listing 16.2.7.5

6.10.2. Clinical Laboratory Evaluations

Clinical laboratory assessments will include hematology, chemistry, coagulation, and urinalysis. Analysis will be performed by the central laboratory. The laboratory evaluation schedule is shown on the Schedule of Assessments (Appendix 13.1).

A descriptive summary of the laboratory results along with change from baseline will be provided.

Shift in clinical laboratory evaluations will be summarized by low, normal and high.

6.10.2.1. Hematology

A descriptive summary of the hematology results along with the change from baseline will be presented. The following laboratory tests will be included in hematology analysis: [redacted]

Shift in abnormality in hematology values will be summarized by minimum and maximum post-baseline abnormal category. Clinical laboratory evaluations will be summarized by low, normal and high.

A listing will present all hematology parameter values for all subjects.

In Mock Shell: Table 14.3.3.1, Table 14.3.3.6 and Listing 16.2.8.1

6.10.2.2. Serum Chemistry

A descriptive summary of the chemistry results along with the change from baseline will be presented. The following laboratory tests will be performed: [redacted]

Liver Function Tests ALT and AST will be presented separately. Other chemistry parameters will be presented separately.

The shift table of liver function tests will be summarized by cohort group for the following categories based on the maximum value of AST and ALT of any post-baseline assessments relative to their baseline categories:

- 1 – 1.5x upper limit of normal (ULN)
- >1.5 – 2.0x upper limit of normal (ULN)
- >2.0 – 3x upper limit of normal (ULN)
- >3.0 – 5x upper limit of normal (ULN)
- >5x upper limit of normal (ULN)

Shift in abnormality in chemistry values other than ALT and AST will be summarized by minimum and maximum post-baseline abnormal category. Clinical laboratory evaluations will be summarized by low, normal and high.

A listing will present chemistry values for all subjects.

In Mock Shell: Table 14.3.3.2, Table 14.3.3.3, Table 14.3.3.7, Table 14.3.3.8 and Listing 16.2.8.2

6.10.2.3. Urinalysis

A descriptive summary of the hematology results along with the change from baseline will be presented. Continuous and categorical summaries will be presented separately.

The following laboratory will be included for urinalysis: [redacted]

pH, specific gravity and urobilinogen values will be summarized.

Shift in abnormality in urinalysis values will be summarized by minimum and maximum post-baseline abnormal category. Clinical laboratory evaluations will be summarized by normal and abnormal.

The urinalysis parameter values will be listed for all subjects in FAS population.

In Mock Shell: Table 14.3.3.4.a, Table 14.3.3.4.b, Table 14.3.3.9 and Listing 16.2.8.3

6.10.2.4. Coagulation

A descriptive summary of the coagulation results along with the change from baseline will be presented. [redacted]

A listing will be provided for coagulation tests by subject and visit.

In Mock Shell: Table 14.3.3.5 and Listing 16.2.8.4

6.10.2.5. Other Laboratory Assessments

[redacted]

Pregnancy test results will be listed by subject.

In Mock Shell: Table 14.3.4.4 and Listing 16.2.8.5

6.10.3. Electrocardiogram

A 12-lead ECG measurement will be obtained using an automatic machine while the subject is in the supine position, after the subject has been resting supine for at least 5 minutes. Electrocardiograms are to be evaluated for clinically significant abnormalities (as defined in section 5.4.10), including [redacted].

Abnormality in ECG parameters collected will be summarized for the following parameters: Ventricular Rate (Beats/Min), P-R Interval (msec), QRS Duration (msec), Q-T Interval (msec), Q-Tc Interval (msec) and overall interpretation.

All ECG results will be listed by dose cohort and subject.

In Mock Shell: Table 14.3.4.1 and Listing 16.2.8.8

6.10.4. Vital Sign Measurements

Vital signs will include body weight, BMI, systolic and diastolic blood pressure, heart rate, respiratory rate and oral body temperature.

Clinically significant abnormities in vital sign measures across all post-baseline assessments as defined in section 5.4.11 are to be summarized for all the parameters.

A descriptive summary of all the vital sign parameters along with change from baseline will be presented by dose cohort.

All vital sign results will be listed by dose cohort and subject. Abnormal results will be highlighted.

In Mock Shell: Table 14.3.4.2, Table 14.3.4.3 and Listing 16.2.8.6

6.10.5. Physical Examination

A full PE will include examination of the head, eyes, ears, nose, and throat (HEENT); skin; and the endocrine, metabolic, neurological, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems. An abbreviated PE will include examination of the skin and respiratory, cardiovascular, and gastrointestinal systems. With each abnormal value, the clinical significance as noted by the investigator will also be included in the listing.

The subject will undergo a full or abbreviated PE at visits shown on the Schedule of Assessments (Appendix 8.1).

All physical examination data collected will be listed.

In Mock Shell: Listing 16.2.8.7

6.11. Other Safety Data

All other safety data that are not in previous sections but that will be collected during the study will be summarized or listed when applicable.

7. References

- Protocol: Adverum Biotechnologies, a Phase 1 / 2 Study of Intravenous or Intrapleural Administration of a Serotype rh.10 Replication Deficient Adeno-associated Virus Gene Transfer Vector Expressing the Human Alpha- 1 Antitrypsin cDNA to Individuals with Alpha-1 Antitrypsin Deficiency (ADVANCE). Amendment 07, 30 Oct 2018.
- [redacted]
- Rangarajan S, Walsh L, Lester W, et al. AAV5–factor VIII gene transfer in severe hemophilia A.N Engl J Med. DOI: 10.1056/NEJMoa1708483
- George LA, Sullivan SK, Giermasz A, et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. N Engl J Med 2017;377:2215-27. DOI: 10.1056/NEJMoa1708538 publications

8. Appendices

8.1. Schedule of Study Procedures (Note: unless specified, all procedures listed below are to be performed for both Part A and Part B)

Note: Unless specified, all procedures listed below are to be performed for both Part A and Part B

Procedure	Pretreament		TX	Follow-up[10]																				
Week			0	1				2	3	4	6	8	10	12	14	15	16	18	20	24	28	32	40	52
Visit number	1	2	3	4	5	6	7	8		9		10		11						12				13
Visit Day	Screening	-1	0	1	2	3	7	14	21															
Visit schedule/window	≤3 mos prior to D0	BL																						or EOS
Informed consent	X																							
Demography	X																							
Medical history	X																							
Inclusion/Exclusion Criteria	X	X																						
Physical exam	X	X																						X
Abbreviated physical exam				X			X			X		X		X						X				
Vital signs	X	X	X	X	X	X	X			X		X		X						X				X
Height	X																							
Weight	X																			X				X
ECG	X																							X
Sample for A1AT genotype[1]	X																							

Procedure		Pretreatment		TX	Follow-up[10]																				
Week				0	1				2	3	4	6	8	10	12	14	15	16	18	20	24	28	32	40	52
Visit number		1	2	3	4	5	6	7	8		9		10		11						12				13
Visit Day		Screening	-1	0	1	2	3	7	14	21															
Visit schedule/window		≤3 mos prior to D0	BL																						[redacted] or EOS
[redacted]																									
Sample for total A1AT level (NephelometryTotal)[3]		X						X																	
Sample for A1AT levels (total & M-type) & function[3]			X					X	X	X	X	X	X	X	X			X		X	X	X	X	X	X
[redacted]																									
Chest x-ray		X																							
Hepatic ultrasound		X																							
Clinical laboratory tests[4]		X	X		X	X		X			X				X						X				X
HIV, HBV, HCV serology[5]		X																							
Pregnancy test[6]		X	X																						X
Part B only	Bronchoscopy & lung ELF sample for A1AT levels and function[7]	X									X										X				

Procedure	Pretreament		TX	Follow-up[10]																				
Week			0	1				2	3	4	6	8	10	12	14	15	16	18	20	24	28	32	40	52
Visit number	1	2	3	4	5	6	7	8		9		10		11						12				13
Visit Day	Screening	-1	0	1	2	3	7	14	21															
Visit schedule/window	≤3 mos prior to D0	BL																						or EOS
[redacted]																								
ADVM-043 administration[8]			X																					
Concomitant medications	X	X	X	X	X	X	X	X		X		X		X						X				X
AEs[9]	X	X	X	X	X	X	X	X		X		X		X						X				X
[redacted]																								
ALT, AST		X[11]						After Day 7, twice weekly to Week 14[12]								X	X	X	X	X	X	X	X	X

Note: X, mandatory procedure; (X), Investigatior discretion.

Abbreviations: A1AT=alpha-1 antitrypsin; AAV=adeno-associated virus; [redacted] AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAL=bronchial alveolar lavage; BL=baseline; ECG=12-lead electrocardiogram; ELF=epithelial lining fluid; HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus; SAE=serious adverse event; TX=treatment; Unsch=unscheduled visit.

1 Only subjects with genotype ZZ or or ZNull are eligible. Genotyping is not required for subjects with documented evidence of genotype.

2 Perform as one of first screening assessments.

3 Sample for total A1AT level to be collected after a minimum 8-week washout period for subjects receiving protein augmentation therapy (PAT) at the Screening Visit. For subjects who resume or start PAT post-treatment, samples for A1AT levels will not continue to be obtained; however, all other safety related parameters (ie, clinical laboratory tests, LFTs, [redacted] and assessment of AEs) will continue to be collected according to the schedule of assessments.

4 Urinalysis, hematology including complete blood count, chemistry, and coagulation. Analysis will be done by the central laboratory.

5 Serology includes: HIV; HBV surface antigen; HCV RNA. Analysis is to be done by the central laboratory.

6 Serum pregnancy test for women of childbearing potential will be performed at Screening; and a urine pregnancy test will be performed at the Baseline and Week 52 visits.

7 Bronchoscopy and BAL will only be performed in Part B.

8 ADVM-043 will be administered by IV infusion in Part-A and by intrapleural injection in Part-B.

9 SAEs that are observed or reported prior to treatment administration should be recorded as SAEs if they are associated with protocol-mandated interventions (invasive procedures such as medication washout, bronchoscopy, or BAL). See Section 7.0 for AE reporting details.

10 Unscheduled visit assessments will be performed at the discretion of the Investigator to ensure the safety of the subject

11 To be performed by the local lab. Treatment may be administered only after test results are available and the LFTs are within the normal range; and the uring pregnancy (if needed) is negative.

12 Bood samples for liver funtion testing (ALT/AST) will be collected at the following frequency:

- twice weekly from Day 7 to Week 14 post-treatment
- once at Weeks 15, 16, 18, 20, 24, 28, 32, 40, and 52