Statistical Analysis Plan

Sponsor Name	Adverum Biotechnologies, Inc.
Protocol ID	ADVM-043-03
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Study Name	ADVM-043-03
Study Title	Post-treatment Long-term Follow-up Study of ADVM-043 Gene Therapy in Alpha-1 Antitrypsin Deficiency
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[redacted]

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Table of Contents

1 Definitions

Abbreviation	Definition
A1AT	Alpha-1 Antitrypsin
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
CRF	Case Report Form
CTM	Clinical Trial Manager
[redacted]	[redacted]
EOS	End-of-Study
FAS	Full Analysis Set
ICF	Informed Consent Form
IE	Inclusion / Exclusion
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MM	Medical Monitoring
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
WHODD	World Health Organization's Drug-Dictionary

2 Introduction

2.1 Background

A clinical research subject who has been exposed to an investigational gene therapy may be at risk for delayed adverse events because of the vector that delivers the transgene or because of persistent biological activity of the investigational medicinal product. Some adverse events could be delayed by months or years. Therefore, to mitigate those risks, and per the United States Food and Drug Administration recommendations for the long-term follow-up observation of subjects who received gene therapy products, Study ADVM-043-03 is to be conducted in subjects previously treated with ADVM-043 and will follow them for a total of 3 years post treatment.

3 Study Objectives

3.1 Primary Objective

Assessment of the long-term safety of ADVM-043

3.2 Secondary Objectives

Not Applicable

4 Study Design

4.1 Overview

Study ADVM-043-03 is a post-treatment long-term follow-up study intended to collect safety data in subjects with A1AT deficiency who received ADVM-043 in a prior treatment study.

No investigational agent will be administered in Study ADVM-043-03.

The study population will comprise of subjects with A1AT deficiency who were previously treated with ADVM-043 in any clinical study.

4.2 Sample Size Justification

Not Applicable.

4.3 Randomization and Blinding

Not Applicable.

4.4 Inclusion/Exclusion Criteria

Inclusion Criteria:

1. *The subject has A1AT deficiency and has previously received ADVM-043 gene therapy.*

Exclusion Criteria:

1. *The subject is unwilling or unable to participate in all required study evaluations*

2. *The subject is participating in another investigational treatment protocol*

3. *The subject is unable to understand the purpose and risks of the study or cannot provide a signed and dated informed consent form (ICF)*

4.5 Treatment Allocation

Not Applicable.

5 Assessment Schedule

Subjects will be assessed for up to 3 years post-treatment with ADVM-043. The duration of this long-term follow-up period is 2 years.

	Post-Treatment Assessment Timepoints			
Assessment [a]	**Screening [b]**	**Year 1** [redacted]	**Year 2** [redacted]	**Year 3 (EOS) [c]** [redacted]
ICF	X			
Inclusion/ Exclusion Criteria	X			
Review and record exposure to other investigational therapies	X	X	X	X
Record AEs of interest/related SAEs	X	X	X	X
Record conmeds [d]	X	X	X	X

Abbreviations: AE = adverse event; conmed = Concomitant medication; EOS = End-of-Study visit; ICF = Informed Consent Form; SAE = serious adverse event; [X] = optional.

[a] Assessments may be conducted in the clinic or with a phone call by site personnel.

[b] The Screening Assessment should be completed on the same day as the End-of-Study Visit in the prior ADVM-043 treatment study.

[c] End-of-Study (EOS) Assessment is scheduled at 3 years post-treatment [redacted]; or within [redacted] after subject withdrawal.

[d] Only concomitant medications for A1AT deficiency (i.e., augmentation therapy), known mutagenic medications / agents, and medications to treat AEs of interest and SAEs related to ADVM-043 should be recorded.

6 Interim Analysis

No interim analysis planned for this study.

6.1 Unblinding and Dissemination of Results

Not applicable.

7 Efficacy and Safety Endpoints

7.1 Primary Endpoint

1. *Type, frequency, severity, duration, and relationship to ADVM-043 of adverse events (AEs) of interest and serious adverse events (SAEs) related to ADVM-043.*

7.2 Secondary Endpoints

Not applicable

8 Statistical Methods

All analyses will be done using SAS (version 9.4, [redacted]).

Safety endpoints will be analyzed in a descriptive manner. Continuous data will be reported using the following descriptive statistics:

1. Number of observations (n)
2. Mean and Standard deviation (SD)
3. Median
4. Minimum (min) and Maximum (max)

Minimum and maximum values will be reported in the units of collection with 3 decimals being maximum value; the mean will be presented with 1 decimal place more and the standard deviation 2 decimal places more than the units of collection. Categorical data will be presented using frequency (n = number of subjects; m = number of events) and percentage (%).

Listings will be provided for all data recorded in eCRF to study subject profiles. All listings will be sorted by cohort, subject ID, and date (if applicable). Unscheduled visit data will only be listed and not included in summaries.

8.1 Handling Missing/Incomplete Data

Missing data will not be imputed.

8.2 Handling Outliers

Not applicable

8.3 Multiplicity Adjustment

Since the study is descriptive in nature, no multiplicity adjustment is required.

9 Analysis Populations

The membership of the analysis populations will be reviewed and finalized during the database lock.

Enrolled set will consist of all subjects who were previously treated with ADVM-043 in any clinical study.

The Full Analysis Set (FAS) consists of all subjects with A1AT deficiency who were previously treated with ADVM-043 in any clinical study and met all the eligibility criteria.

10 Analysis Variables

10.1 Population Flags

Population flags will be finalized and authorized by the Study Statistician and Sponsor during data review meeting prior to database lock as per definitions provided in Section 9. These flags will be included in the analysis datasets.

10.2 Treatment groups

Subjects from ADVM-043-01 study will be enrolled into this follow-up study and the summaries will be created based on the same cohorts as ADVM-043-01 study.

All analyses will be summarized by cohort. The following cohorts will be defined in the analysis datasets. All doses in numeric format will also be included as core variable.

- Cohort 1 (8×10^{13} vg)
- Cohort 2 (4×10^{14} vg)
- Cohort 3 (1.2×10^{15} vg)

10.3 Visits

All analysis datasets with measurements taken at more than one visit will have analysis visit as defined below.

- Screening
- Year 1
- Year 2
- Year 3 (EOS)
- Early Termination

The Screening Assessment should be completed on the same day as the End-of-Study Visit in the prior ADVM-043-01 treatment study.

10.4 Protocol Deviations

A significant deviation is defined as a protocol deviation that affects primary assessments, the safety of a subject or the scientific value of the trial ([redacted]). Significant deviations can include non-adherence to entry criteria; enrollment of the subject without prior Sponsor approval; or non-adherence 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 by the Clinical Trial Manager (CTM) and the Medical Monitoring (MM) team.

Any difference in the deviations classification will be discussed and finalized before the database lock. The protocol deviation summaries will be presented accordingly.

Deviation codes:

Deviations will be coded by the Clinical Trial Manager (CTM) and the Medical Monitoring (MM) team as below.

- Inclusion
- Exclusion
- Assessment – safety
- Visit window
- Informed consent
- Other

10.5 Study Duration

Study Duration (years) = ((Date of Last Visit – Date of Informed Consent) + 1)/365.25.

10.6 Adverse Events Flags

An AE is any untoward medical occurrence in an enrolled subject, regardless of its causal relationship to the investigational medicinal product.

Only AEs of interest will be collected and reported in the current study. AEs of interest that are continuing from the previous study will be imported for long term follow-up.

AEs of interest include:

- new malignancy
- new incidence or exacerbation of a pre-existing neurologic disorder
- new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- unexpected hospitalization

Study Period:

All AEs will be counted once under the below period in which the AE has started.

- Previous Study: Reported from AE (External).
- Screening – Year 1: If AE start date is after screening and on or before Year 1 visit date.
- Year 1 – Year 2: If AE start date is after Year 1 and on or before Year 2 visit date.
- Year 2 – Year 3 (EOS): If AE start date is after Year 2 and on or before Year 3 visit date.

Related Adverse Events:

- AE (External): includes Possibly, Probably and Definitely Related Adverse Events
- AE: includes Definitely and Likely Related Adverse Events.

Relationship to ADVM-043 will be flagged separately.

Severity:

Subjects with the same AE of interest 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'. AEs that are missing severity will be presented in summary tables as 'Grade 3 – Severe'.

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

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

11 Statistical Analyses

11.1 Subject Disposition

Number of subjects in enrolled, screen failures and in FAS population, number and percentage for subjects who completed the study, study duration (years)[10.5], number of subjects who discontinued the study early along with their reasons will be summarized by cohort. Reason for discontinuation will be displayed in the descending order of "Total" column.

Reason for not completing the study includes:

- A medical decision is made to resume or initiate
- Lost to Follow up
- Withdrawal of consent by Subject
- Adverse event
- Major Protocol deviation prior to treatment

- Physician Decision
- Study Terminated by Sponsor
- Other

Percentages will be based on FAS population.

Number of subjects who did not meet the IE criteria will be summarized separately. Percentages will be based on enrolled population.

[redacted]

Subject disposition information, status of inclusion exclusion criteria will be listed by subject.

[redacted]

11.2 Visit Attendance

Number and percentage of subjects who attended each visit (Screening, Year 1, Year 2, and Year 3 (EOS)) will be summarized by cohort. Percentages will be based on FAS Population.

[redacted]

11.3 Protocol Deviations

Significant protocol deviations:

Number and percentage of subjects with any significant protocol deviation along with their categories will be summarized by cohort.

Percentages will be based on FAS population.

[redacted]

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.

[redacted]

11.4 Subject Demographics

Subject demographics will be summarized by cohort. Categorical and continuous variables will be provided in the same table. The following variables will be presented: age (years), sex, ethnicity and race.

Percentages are based on FAS population.

[redacted]

Subject demographics will be listed by subject.

[redacted]

11.5 Concomitant Medications

Number and percentage of subjects who have taken any medication and number of medications will be summarized by cohort. Number of patients who have taken any medication will be classified by Therapeutic Main group (ATC Level 2) and Chemical Substance group (ATC Level 5). The therapeutic main group and chemical substance group will be displayed in the descending order of frequency in "Total". Medications will be coded using the World Health Organization's Drug-Dictionary (WHODrug Dictionary) version B2 Enhanced VSEP 2017 or higher.

Percentages will be based on FAS population.

[redacted]

All medications will be listed by subject and therapeutic subgroup.

[redacted]

11.6 Extent of Exposure

IMP administration data will be listed by subject for FAS population. Subjects will be grouped by cohort.

[redacted]

11.7 Safety Analyses

The long-term safety of ADVM-043 is to be assessed by determining the type, frequency and percentages, severity, duration, and relationship to ADVM-043 of adverse events (AEs) of interest and serious adverse events (SAEs) related to ADVM-043. All safety data will be listed and summarized by cohort using the FAS population.

Only AEs of interest will be summarized.

11.7.1 Adverse Events

All Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or Higher. All summaries will be based on FAS population.

11.7.1.1 Overall Adverse Events

Number and percentage of subjects will be summarized by cohort for the following categories:

1. All adverse events of interest reported
2. ADVM-043 related adverse events
3. Adverse events ≥ grade 3
4. Serious adverse events
5. ADVM-043 related serious adverse events
6. Fatal adverse events

Percentages will be based on FAS population.

[redacted]

All adverse events will be listed by subject and system organ class. Adverse events will be grouped by subject. Duration of AEs will also be included in the listing.

[redacted]

11.7.1.2 Summary of Adverse Events of Interest by SOC and PT

Number and percentage of subjects will be summarized by cohort, system organ class and preferred terms. Percentages will be based on FAS population. Events will be displayed in the descending order of frequency in “Total”.

The same will be repeated for ADVM-043 related AEs of interest, Serious AEs of interest, ADVM-043 related serious AEs.

[redacted]

Listings for ADVM-043 related AEs of interest, serious AEs of interest will be listed similar to Listing 16.2.7.1 with respective information.

Death due to AEs will also be listed separately.

[redacted]

11.7.1.3 Summary of Adverse Events by Severity

Number and percentage of subjects in each system organ class, preferred term, and intensity (Grade 1-5) will be summarized by severity for adverse events of interest and cohort. System organ class and preferred term will be displayed by descending order of frequency in “Total”.

[redacted]

12 Changes to Planned Analyses

No changes from the analysis defined in protocol.

13 Index of Tables, Listings and Graphs

Refer [redacted] for the list of Tables, Listings and Graphs.

14 References

Provide list of references used to create this document.

- ICH. ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials E9. 1998.
- ASA. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics. 1999.
- ICH. ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports E3. 1995.

15 Appendices

Not Applicable

16 Change Log

Version	Authored by	Change Date	Change Details	Reviewed by	Review Date
1.0	[redacted]	[redacted]	First Draft	[redacted]	[redacted]