CLINICAL STUDY PROTOCOL

ADVERUM
BIOTECHNOLOGIES

Clinical Protocol No.	ADVM-043-03
Study Title	Post-treatment Long-term Follow-up Study of ADVM-043 Gene Therapy in Alpha-1 Antitrypsin Deficiency
Sponsor	Adverum Biotechnologies, Inc. [redacted]
Investigational Product	ADVM-043
Indication Studied	Alpha-1 Antitrypsin Deficiency

Protocol Version	Document Identifier / Effective Date
Original	ADVM-043-03 / [redacted]
Amendment 01	A1 v [redacted] / [redacted]
Amendment 02	A2 v.15.08.2019 / 15 Aug 2019

PROTOCOL APPROVAL—ADVERUM SIGNATORY

Protocol ID	ADVM-043-03
Study Title	Post-treatment Long-term Follow-up Study of ADVM-043 Gene Therapy in Alpha-1 Antitrypsin Deficiency

Study ADVM-043-03 will be conducted in accordance with the ICH and Harmonized Tripartite Guidelines for Good Clinical Practices (E6), with applicable local regulations, including US Code of Federal Regulations [CFR] Title 21, and the ethical principles outlined in the Declaration of Helsinki.

Protocol approved by:

[redacted]

INVESTIGATOR AGREEMENT

I have read this clinical protocol as set forth below. On behalf of myself and the study staff, I agree to conduct Study ADVM-043-03 in compliance with the terms of the protocol as outlined herein and in compliance with Good Clinical Practice (GCP) and all applicable legal and regulatory requirements. Furthermore, I understand that the Sponsor, Adverum Biotechnologies, Inc, and the Independent Ethics Committee / Institutional Biosafety Committee (IEC / IBC) must approve any changes to the protocol in writing before implementation, except where it may be necessary to eliminate an immediate hazard to a subject enrolled in this study. I agree not to divulge to anyone, either during or after the study, any confidential information acquired regarding the investigational medicinal product and processes or methods of Adverum. All data pertaining to this study will be provided to Adverum.

_____ _____

Principal Investigator (Signature) Date

Printed Name:

Institution:

Address:

ADVM-043-03 CONTACT LIST

Sponsor	Adverum Biotechnologies, Inc. [redacted]
Sponsor's Medical Monitor	[redacted]

STUDY SYNOPSIS

Study ID:	ADVM-043-03
Study Title:	Post-treatment long-term follow-up study of ADVM-043 gene therapy in alpha-1 antitrypsin deficiency
Sponsor:	Adverum Biotechnologies, Inc.
Indication:	Alpha-1 Antitrypsin (A1AT) Deficiency
Phase of Development:	2
Objectives:	Primary objective • Assessment of the long-term safety of ADVM-043
Endpoints:	Primary endpoint • Type, frequency, severity, duration, and relationship to ADVM-043 of adverse events of interest and serious adverse events related to ADVM-043
Study Design:	This is a long-term follow-up study in subjects with A1AT deficiency who have previously received ADVM-043 gene therapy in a clinical study. Subjects will be followed for up to 3 years post-treatment with ADVM-043.
Study Duration:	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.
Entry Criteria:	<u>Inclusion Criteria</u> 1) The subject has A1AT deficiency and has previously received ADVM-043 gene therapy <u>Exclusion Criteria</u> 1) The subject is unwilling or unable to participate in all required study evaluations 1) The subject is participating in another investigational treatment protocol 2) The subject is unable to understand the purpose and risks of the study or cannot provide a signed and dated informed consent form (ICF)

Study Population:	Subjects with A1AT deficiency who were previously treated with ADVM-043 in any clinical study
Safety Evaluation:	Evaluations will include assessment of adverse events

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LIST OF ABBREVIATIONS

Abbreviation or Term	Expanded term or definition
A1AT	Alpha-1 Antitrypsin
AAV	Adeno-Associated Virus
AE	Adverse Event
CRF	Case Report Form
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
SAE	Serious Adverse Event
EOS	End-of-Study visit
IEC	Independent Ethics Committee
IBC	Institutional Biosafety Committee

1.0 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.

The advantage of adeno-associated viral (AAV) vectors in gene therapy is the low propensity of vector genome integration in the host DNA. However, recently there has been attention to potential AAV-induced genotoxicity from systemic or liver-directed gene therapy. To date, mouse studies have varied in their findings in neonatal, juvenile, and adult animals.

AAV genome integration has been observed in neonatal mice that demonstrated a higher risk of developing hepatocellular carcinoma after AAV administration (Bell 2005; Chandler 2015). This insertional mutagenesis to an oncogenic locus (Rian) reported after neonatal gene delivery is thought to be influenced by higher transcriptional activity of that locus during the neonatal period of development, as juvenile and adult rodents have not demonstrated similar findings. Furthermore, the site of AAV integration in mice has no analogue in humans (Bell 2005; Chandler 2015). Long-term larger animal studies in dogs (through 8 years) and nonhuman primates (through 5 years) have not shown such genotoxicity (Niemeyer 2009; Nathwani 2011).

To date, there has been no evidence of tumor formation or long-term hepatotoxicity in a hemophilia B gene therapy trial where 10 subjects were treated with systemic AAV. The study demonstrated durable and stable expression of transgenic factor IX at therapeutic levels for at least 4 years after vector delivery (Nathwani 2014).

In alpha-1 antitrypsin (A1AT) deficiency, intramuscular delivery of an AAV1 vector containing a functional A1AT transgene was administered to 18 human subjects (Gruntman 2015). One of the subjects in the highest dose group followed for at least 5 years post-treatment for safety and protein expression still demonstrated measurable A1AT levels without any negative sequelae (Mueller 2017). This suggests gene therapy has the potential for long-term protein expression and consequent disease impact. [redacted]

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.

1.1 Study Population

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

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective:

- Assessment of the long-term safety of ADVM-043

2.2 Endpoints

2.2.1 Primary Endpoint

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

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a long-term follow-up study in subjects with A1AT deficiency who have previously received ADVM-043 gene therapy in a clinical study. Subjects will be followed for up to 3 years post-treatment with ADVM-043.

3.2 Study Duration

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.

3.3 Study Termination

The Sponsor reserves the right to terminate the study, or any part of the study, at its discretion for any reason. Should this be necessary, both the Sponsor and the Investigator will arrange the discontinuation procedures. If this study is terminated, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subject's interests.

3.4 Concomitant Medications

There are no prohibited medications.

Any use of protein augmentation therapy for the treatment of A1AT deficiency should be recorded in the case report form (CRF), including any change in its use, such as initiation, discontinuation, holding the dose or change in dosage.

Exposure to known mutagenic medications or agents (Appendix 2) should be recorded in the CRF.

Concomitant medications used to treat AEs of interest and SAEs related to ADVM-043 are to be recorded in the CRF. Other concomitant medications do not need to be recorded.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

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

4.2 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).

4.3 Subject Withdrawal

A subject may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the clinical study site.

Withdrawal from the study will occur under the following circumstances:

- Death
- Withdrawal of consent
- Lost to follow-up
- Study termination by Sponsor

If a subject is lost to follow-up, a minimum of two attempts should be made by the study site personnel to contact the subject. Appropriate contact includes 2 documented phone calls followed by a registered letter before a subject may be listed as lost to follow-up. The measures taken for follow-up and reason for premature study discontinuation should be documented in source documents and CRF.

When a subject withdraws from the study, the reason(s) for withdrawal are to be recorded on the CRF. Whenever possible, all subjects who withdraw from the study are to be encouraged to undergo the End-of-Study assessments at the time of withdrawal.

Sites should obtain follow-up data on any subject who withdraws from the study and has ongoing AEs of interest or SAEs related to ADVM-043. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

5.0 STUDY ASSESSMENTS

Assessments may be conducted in the clinic or remotely via telephone call by site personnel. A subject is required to sign an IRB/IEC approved ICF before any study assessments are performed. Refer to the Schedule of Assessments in Appendix 1.

5.1 Screening Assessment

The Screening Assessment should be completed on the same day as the End-of-Study Visit in the prior ADVM-043 treatment study, irrespective of whether the subject completes the prior treatment study.

The following evaluations are to be conducted at the Screening Assessment:

- Informed consent
- Review of inclusion/exclusion criteria (re-confirm prior to enrollment at the Year 1 assessment)

5.2 Year 1 Assessment through Year 2 Assessment

At each assessment, the following evaluations will be conducted:

- Review and record AEs of interest (Section 6.2), including type, frequency, severity, and relationship to ADVM-043
- Review SAEs related to ADVM-043 including type, frequency, severity
- Review and record any use of augmentation therapy, including any change in its use, such as initiation, discontinuation, holding dose, or change in dosage
- Review and record any exposure to known mutagenic medications or agents (Please refer Appendix 2 Mutagenic Medications / Agents)
- Review and record if the subject has been exposed to any new investigational therapies since the last assessment

6.0 ASSESSMENT OF SAFETY

6.1 Safety Parameters

- Adverse events

6.2 Definition of an Adverse Event

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 should be collected and reported.

AEs of interest include the following:

- 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

6.3 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence in an enrolled subject that results in death; is immediately life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; or is a congenital anomaly or birth defect. Only SAEs related to ADVM-043 should be collected and reported.

6.4 Assessment of Severity

The severity or intensity of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated according to the Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute 2017):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living (bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent do not require documentation of onset and duration of each episode.

6.5 Assessment of Causality

The Investigator's assessment of relationship of an AE to ADVM-043 is part of the documentation process, but it is not a factor in determining what is or is not reported. If there is any doubt as to whether a clinical observation is an AE, the event is to be reported.

Investigator should assess potential causes of each AE and events should be considered related if there is "a reasonable possibility of a causal relationship" rather than if "a causal relationship cannot be ruled out." When assessing causality, Investigators should assess biological balancing — the probability that the suspect drug caused the AE must be weighed against the probability that an alternative candidate caused it.

Causality of AEs should be assessed in relation to ADVM-043, and not prior concomitant medications or study procedures in the previous treatment study. The relationship or association of ADVM-043 in causing or contributing to the AE is to be characterized using the following criteria:

- Definitely Related: A definite causal relationship exists between study drug administration and the AE; including a plausible time relationship to study drug administration, and it cannot be explained by underlying or concurrent disease or other drugs/exposures.

- Likely Related: There is a reasonable possibility that the study drug caused the AE; the event is unlikely attributed to underlying or concurrent disease or other drugs/exposures (i.e., alternative explanation). There is a reasonable time sequence to administration of the study drug.

- Unlikely Related: Underlying or concurrent disease or other drugs/exposures provide plausible alternative explanations. Temporal relationship to study drug administration makes a causal relationship improbable.

- Not Related: There is no association between the study drug and the reported event; there is a clear alternative explanation; a causal relationship is non-plausible.

6.6 Safety Assessment Method and Timing

At each study assessment conducted either in the clinic or by telephone, the Investigator or designee will ask the subject non-leading questions to obtain reports of any change in medical condition or diagnosis consistent with the AEs of interest or SAEs related to ADVM-043 (Section 6.2 and Section 6.3).

A plan for scheduled visits with an HCP to elicit and record new findings for each study subject, including history, physical examination, or laboratory testing will be included in the study manual in accordance with the FDA guidance on the design of long term follow-up observational studies for the collection of data on delayed adverse events following administration of gene therapy products (FDA Draft Guidance for Industry 2018).

Information to be collected includes event term per CTCAE Version 5.0 (National Cancer Institute 2017); date of onset; Investigator assessment of seriousness, severity, and relationship to ADVM-043; date of resolution of the event; any required concomitant medication or treatment; evaluations for malignancies and results such as biopsy results; and outcome.

6.7 Adverse Event Reporting

The Investigator or designee is to be responsible for collecting all events that meet the definition of AEs of interest (Section 6.2). AEs of interest should be recorded on the CRF by the Investigator or designee

6.8 Serious Adverse Event Reporting

SAEs related to ADVM-043 should be recorded on the CRF by the Investigator or designee (Section 6.3). The Investigator must report a related SAE to the Sponsor within 24 hours of awareness of the event to meet regulatory and patient safety obligations. For additional details on reporting of safety reports please refer to the Investigator Study Manual.

6.9 Follow-up of Subjects Reporting an Adverse Event

SAEs related to ADVM-043 and AEs of interest should be followed until satisfactory resolution or until the Investigator deems the event to be stable.

6.10 Request for Autopsy in the Event of a Subject Death

In the event of a subject death while participating in the study, the Investigator should request a full autopsy to determine the precise cause of death. If possible, samples of tissues obtained at autopsy should be evaluated for the presence of the AAV genome.

7.0 ASSESSMENT OF EFFICACY

Not applicable

8.0 STATISTICAL PLAN

Descriptive and exploratory analyses are to be performed on all data to gain insight into the safety of ADVM-043. Adverse event data are to be analyzed overall, by dose level administered, and by study. Refer to the Statistical Analysis Plan.

9.0 ETHICAL CONSIDERATIONS

9.1 Independent Ethics Committee / Institutional Biosafety Committee

Federal regulations and the ICH guidelines require that approval be obtained for each clinical site from an independent ethics committee / institutional biosafety committee (IEC / IBC) before participation of human subjects in research studies. Before study onset, the protocol, informed consent form, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IEC / IBC, and written confirmation of such approval must be received by the site. Documentation of all approvals and of the IEC / IBC compliance with ICH Guideline for Good Clinical Practice (E6) will be maintained by the site and will be available for review by the Sponsor or its designees.

All approvals should be signed by the IEC / IBC chair or designee and must identify the IEC / IBC by name and address, the clinical protocol by title or protocol number or both, and the date approval or favorable opinion was granted.

9.2 Ethical Conduct of the Study

The study is to be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and Council of International Organizations of Medical Sciences (CIOMS) Ethical Guidelines, and in accordance with the International Council for Harmonization (ICH) Harmonized Tripartite Guideline E6: Good Clinical Practice; 21 CFR; and applicable laws and regulations.

This study will be conducted in compliance with the protocol approved by the IEC / IBC, and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and the IEC, except where it may be necessary to eliminate an immediate hazard to a subject enrolled in this study. In such case, the deviation will be reported to the IEC as soon as possible.

9.3 Subject Information and Consent

The study-specific informed consent form (ICF) and the informed consent process must comply with the Declaration of Helsinki, US Title 21 Code of Federal Regulations (CFR) Part 50, HIPAA (if applicable), and local laws. The Investigator will draft the informed consent form, assent, and HIPAA authorization (if applicable) and submit the draft for review and comment by the Sponsor, and Investigator will submit the mutually agreed upon ICF, ascent, and HIPPA authorization (if applicable) to the IEC/IBC for approval.

The Investigator or designee (designee listed on the Delegation of Responsibilities log) must explain in terms understandable by the subject the content of the informed consent form including the purpose and nature of the protocol, procedures, anticipated benefit, potential risks, possible AEs, and any discomfort that participation in the protocol may entail. This process must be documented in the subject's source record. Each subject or legally acceptable representative must be allowed to read the ICF under conditions where there is adequate time to consider the risks and benefits associated with participation.

Before any study-specific procedure or test is performed, the Investigator must be certain that the subject or legally acceptable representative understands the implications of participation in the study. The subject or legally acceptable representative and the Investigator must sign and date the ICF before such subject is entered into the study. The Investigator is to retain the signed ICF and give a copy of the signed form to the subject or legally acceptable representative. The process of obtaining informed consent is to be documented in the subject's records.

The Investigator or designee shall maintain a log of all subjects who have signed ICF, or whose legally acceptable representative has signed the ICF; and indicate whether the subject was enrolled or the reason for non-enrollment.

If the ICF is revised during the study, any institution-specific modifications proposed by the site should be reviewed and approved by the Sponsor or designee before IEC submission.

10.0 INVESTIGATOR'S RESPONSIBILITIES

A complete list of Investigator responsibilities is outlined in the Clinical Trial Agreement and, for US Investigators, the Statement of Investigator Form FDA 1572, signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol, the Statement of Investigator, the general investigational plan, and applicable laws and regulations; will read and understand the Investigator's Brochure; will obtain IEC / IBC approval to conduct the study; will obtain informed consent from each study participant prior to their participation in the study; will maintain and supply to the Sponsor or designee, auditors, and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IEC / IBC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IEC / IBC according to the specifics outlined in this protocol, which reports shall include an assessment of whether there is a reasonable possibility that the study drug caused the AE; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

11.0 SPONSOR RESPONSIBILITIES

A complete list of the Sponsor responsibilities is outlined in the Clinical Trial Agreement and in the laws and regulations of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, ensure that each Investigator conducts the study in accordance with the general investigational plan and protocol, and promptly inform Investigators and health and regulatory agencies as appropriate of significant new adverse effects or risks with respect to the drug.

11.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to a subject, must be reviewed and approved by the Sponsor prior to implementation. Protocol Amendments must be approved by the IEC / IBC before any subject can be enrolled into an amended protocol.

11.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the procedures and processes as specified in the protocol. A significant protocol deviation occurs when there is nonadherence to the protocol that might significantly (a) impact the completeness, reliability, and / or accuracy of the study data, or (b) affect a subject's rights, safety, or well-being. The Investigator or designee must document and explain any protocol deviation in the subject's source documentation. Any significant protocol deviation will be investigated and reported by the Sponsor and may lead to the subject being withdrawn from the study, termination of the Investigator's participation in the study, and / or other actions.

The Sponsor will be notified of known significant protocol deviations by the Investigator. Protocol deviations found throughout the course of monitoring visits are to be documented by the clinical monitor. The IEC / IBC should be notified of all protocol deviations in a timely manner by the Investigator.

11.3 Confidentiality

Investigators must comply with all applicable privacy laws and regulations (e.g., HIPAA). Information on maintaining subject confidentiality in accordance with individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process, either as part of the ICF or as a separate signed document. In the United States, a site-specific HIPAA-compliant authorization form may be used. The Investigator or designee must explain to each subject that for the evaluation of study results and potential marketing approval, the subject's protected health information obtained during the study may be disclosed to the Sponsor and its designees, regulatory agencies, and the IEC / IBC.

It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject or used or disclosed except as necessary to protect the integrity of the study. Any data collected on the subject before withdrawal will be used by Sponsor and / or its designees in the analysis of study results in order to protect the integrity of the study. During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected in accordance with applicable professional standards and regulations.

11.4 Investigator's Report to the IEC / IBC

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IEC / IBC.

Upon completion of the study, the Investigator, where applicable, should submit to the IEC / IBC the summary of the study outcome.

11.5 Records Retention

The Investigator is responsible for retaining documents as required by local law and applicable regulations, as well as ICH standards. Essential documents should be retained until [redacted] after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until [redacted] have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.6 Financial Disclosure

[redacted] For this study, each principal Investigator and sub-Investigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with 21 CFR Part 54. Each Investigator will notify the Sponsor or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

11.7 Liability and Insurance

[redacted]

In the event of a side effect or injury, appropriate medical care as determined by the treating physician/designee will be provided. The ICF will include a description of treatment in the event of a protocol-related injury and handling of the costs associated therewith, incorporating country-specific national regulations and / or local laws. [redacted]

12.0 STUDY MANAGEMENT

12.1 Monitoring of the Study

All aspects of the study will be monitored by the Sponsor or designee for compliance with applicable government regulation with respect to GCP and standard operating procedures.

Investigators and institutions involved in the study will permit study-related monitoring, audits, IEC review, and regulatory agency inspections, including by providing direct access to all study records.

In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or applicable regulatory agencies an access to all study records. The Investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports to the Sponsor.

12.2 Data Quality Assurance

The Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted, and that data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with the Food and Drug Administration (FDA) regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D—Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

12.3 Data Management

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

The Investigator or other study personnel will enter information from the source documents onto case report forms (CRFs) that will be used to collect the clinical study data. A CRF must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physicians' notes, nurses' notes, clinic charts, and other study-specific source documents).

Authorized study site personnel (i.e., listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

Study staff will be appropriately trained in the use of CRFs.

The Investigator attests that the information contained in the CRFs is true by providing signature within the data capture system.

After database lock, the Investigator will receive a copy of the subject data (e.g., paper, CD, or other appropriate media) for archiving at the study site.

13.0 STUDY COMPLETION

The study is expected to be completed at the timepoint when all subjects have completed or exited the protocol for any reason, or the protocol is terminated at the Sponsor's discretion, whichever occurs first.

14.0 REFERENCES

Bell P, Wang L, Lebherz C, et al. No evidence for tumorigenesis of AAV vectors in a large-scale study in mice. Mol Ther. 2005;12(2):299-306.

FDA Draft Guidance for Industry (For Comment Purposes Only): Long Term Follow-Up After Administration of Human Gene Therapy Products. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; July 2018.

Chandler RJ, LaFave MC, Varshney GK, et al. Vector design influences hepatic genotoxicity after adeno-associated virus gene therapy. J Clin Invest. 2015;125(2):870-880.

Gruntman AM, Flotte TR. Progress with recombinant adeno-associated virus vectors for gene therapy of alpha-1 antitrypsin deficiency. Hum Gene Ther Method. 2015;26(3):77-81.

Mueller C, Gernoux G, Gruntman AM, et al. 5 year expression and neutrophil defect repair after gene therapy in alpha-1 antitrypsin deficiency. Mol Ther. 2017;25(6):1387-1394.

Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. The New England journal of medicine. 2014;371(21):1994-2004.

Nathwani AC, Rosales C, McIntosh J, et al. Long-term safety and efficacy following systemic administration of a self-complementary AAV vector encoding human FIX pseudotyped with serotype 5 and 8 capsid proteins. Mol Ther. 2011;19(5):876-885.

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Niemeyer GP, Herzog RW, Mount J, et al. Long-term correction of inhibitor-prone hemophilia B dogs treated with liver-directed AAV2-mediated factor IX gene therapy. Blood. 2009;113(4):797-806.

15.0 APPENDICES

15.1 Appendix 1 Schedule of Assessments

	Post-Treatment Assessment Timepoints			
Assessment [a]	**Screening [b]**	**Year 1 [b]** [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.

15.2 Appendix 2 Mutagenic Medications / Agents

Classes of mutagenic medications / agents include, but are not limited to:

- alkylating agents (e.g., cyclophosphamide)
- anthracyclines (e.g., doxorubicin)
- platinum-based agents (e.g., carboplatin)
- retinoids (e.g., tretinoin)
- vinca alkaloids (e.g., vincristine)
- topoisomerase inhibitors (e.g., etoposide)
- antimetabolites / nucleotide analogues (e.g., methotrexate)
- aromatic hydrocarbons (e.g., benzene)
- toxic heavy metals and metalloids (e.g., arsenic)