CLINICAL STUDY PROTOCOL

Study ID	**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)
Indication Studied	Alpha-1 Antitrypsin Deficiency
IND Number	016008

Study ADVM-043-01 is to be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Protocol Version	Document Identifier/ Effective Date
Original	A0[redacted]
Amendment 01	A1[redacted]
Amendment 02	AM[redacted]
Amendment 03	AM[redacted]
Amendment 04	AM[redacted]
Amendment 05	AM[redacted]
Amendment 06	AM[redacted]
Amendment 07	AM v.10.30.18

ADVM-043-01 Amendment 7 Contact list

Sponsor	Adverum Biotechnologies, Inc.
	[redacted]
Sponsor's Medical Monitor	[redacted]
SAE 24-hour hotline	[redacted]

Protocol Approval—Adverum Signatory

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)
Protocol Number / Date	ADVM-043-01 Amendment 7 30 Oct 2018

This study will be conducted with the highest respect for the individual patients in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- The International Council of Harmonisation and the Harmonised Tripartite Guideline for the Good Clinical Practice I
- All applicable laws and regulations, including, but not limited to, data privacy laws and regulations.

Protocol accepted and approved by:

[redacted]

Declaration of the Investigator

I have read and understood all sections of the protocol entitled "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).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol; the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline E6: Good Clinical Practice; 21CFR and applicable laws and regulations; and the Declaration of Helsinki and Council of International Organizations of Medical Sciences (CIOMS) Ethical Guidelines.

I will not make changes to the protocol before consulting with Adverum Biotechnologies, Inc. or implement protocol changes without independent ethics committee approval, except to eliminate an immediate risk to a subject. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a sub-investigator.

I will not supply ADVM-043 to any person not eligible to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Adverum Biotechnologies, Inc.

Name and Signature of Principal Investigator	Date
Affiliation	

Protocol Synopsis

Study ID	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)
Sponsor:	Adverum Biotechnologies, Inc.
Study Phase:	Phase 1/2
Sample Size:	The total number will range between 2 and 25 subjects.
Study sites:	Approximately 5 clinical trial sites in the United States
Indication:	Alpha-1 antitrypsin (A1AT) deficiency
Rationale:	Study ADVM-043-01 is intended to assess the hypothesis that administration of an adeno-associated viral (AAV) serotype rh.10 (AAVrh.10) vector expressing the human M-type A1AT (ie, ADVM-043) to individuals with A1AT deficiency is safe and results in persistent therapeutic levels of A1AT in blood and alveolar epithelial lining fluid (ELF). 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 for eventual marketing authorization approval of this therapy.
Objectives:	Primary • To assess the safety of ADVM-043 following intravenous administration Secondary • To assess the effect of ADVM-043 on plasma A1AT concentrations following intravenous administration • To assess the safety and effect of ADVM-043 following intrapleural administration

Endpoints

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

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]

Study Design:

Study ADVM-043-01 is a Phase 1/2, open-label, multicenter, dose-escalation clinical study to evaluate the safety and treatment effect of ADVM-043, an investigational medicinal product (IMP), in subjects with A1AT deficiency. In Part A of the study, ADVM-043 will be administered by intravenous (IV) infusion. In Part B of the study, ADVM-043 will be administered by intrapleural injection. Safety and efficacy data from Part A, including maximum tolerated dose (MTD), will be considered when determining whether to proceed to Part B and the dose-level to be delivered.

Each subject is to receive a single dose of ADVM-043. Up to 4 dose levels are to be tested in Part A and 1 dose level in Part B, pending occurrence of dose-limiting toxicities and efficacy seen at each dose-level. Following treatment with ADVM-043, each subject is to be monitored for safety and treatment effect outcomes over a period of 1 year. [redacted]

[redacted].

A Data Monitoring Committee (DMC) will be involved in the study to ensure the safety of all subjects who have been administered ADVM-043. Before each potential dose-escalation, the DMC will review the by-subject safety and efficacy data, as appropriate, and confirm any dose-limiting toxicities that were determined by the investigator. A dose-limiting toxicity (DLT) is defined as an adverse event (AE) with severity Grade ≥3 by CTCAE criteria deemed by the Investigator to be attributable to ADVM-043 and that occurs within the DLT observation period. The DLT observation period for the first (sentinel) subject is 6 weeks following dosing in each dosing cohort and for the second or any subsequent subject, 4 weeks following dosing.

Enrollment will be suspended and appropriate regulatory authorities will be notified 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)

Any event that meets any of the above safety stopping criteria will be reported immediately to the Sponsor and enrollment and dosing will be temporarily suspended until the risk to the subjects is mitigated.

The event will also be reported immediately to the appropriate regulatory authorities. The DMC will meet on an ad hoc basis to review and assess the event and it will be the responsibility of the DMC to make a recommendation to the Sponsor if they believe that enrollment should be suspended. The regulatory authorities and the Investigators, and each site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and other appropriate institutional regulatory bodies will be promptly notified by the Sponsor if a decision to suspend enrollment is made.

If study enrollment is suspended, all subjects who have already been treated will remain in the study and will continue to be monitored through their completion or withdrawal from the study.

All AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

In terms of efficacy, changes in plasma A1AT levels over baseline will provide evidence of activity of ADVM-043. Plasma A1AT levels will be measured prior to study treatment and at Day7, 14, and 21; and at Weeks 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 40 and 52 post study treatment. Therefore, subjects are to be treatment-naïve to protein augmentation therapy (PAT) or to have stopped receiving PAT at least 8 weeks prior to study treatment administration. PAT should not be administered through the Week 12 visit. However, the treating

physician in consultation with the Adverum Medical Monitor may make a determination 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 (ie, clinical laboratory tests, LFTs, [redacted] and assessment of AEs) according to the schedule of assessments.

Subject Population:

Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Capable of providing informed consent
2. Males and females ≥18 years of age
3. A1AT genotype ZZ or Z Null. Genotyping does not need to be performed for subjects for whom documented evidence of genotype from a qualified diagnostic lab is provided
4. Plasma A1AT level <11 µM prior to the Baseline Visit
5. Any subject receiving A1AT protein augmentation therapy (PAT) must be willing to washout. Washout is defined as at least 8 weeks between last PAT dose and pre-treatment plasma A1AT level.
6. Willing to remain off PAT for at least 3 months following treatment (Day 0)
7. Body mass index of 18 to 35 kg/m^2
8. Men and women of childbearing potential should agree to use barrier contraception for 3 months after treatment (Day 0)
9. Willing to participate in all study procedures and attend scheduled study visits

Exclusion Criteria

Subjects meeting any of the following criteria are to be excluded:

1. Forced Expiratory Volume in 1 Second (FEV1) < 35 percent of predicted value at the Screening visit
2. Receiving systemic corticosteroids or other immunosuppressive medications
3. Immunodeficiency disease or evidence of active infection of any type, including human immunodeficiency virus
4. Evidence of major central nervous system, major psychiatric, musculoskeletal, or immune disorder
5. History of myocardial infarction within the past 1 year
6. History of cancer within the past 5 years, other than treated nonmelanomatous carcinoma of the skin and treated carcinoma in situ (CIS) of the cervix

7. Any clinically relevant abnormality evidenced by the screening hepatic ultrasound and/or chest x-ray
8. Within 24 hours of study treatment administration, evidence of active infection deemed clinically significant by the Investigator based on clinical exam and/or temperature > 38.5°C
9. Creatinine > 2 mg/dL
10. Alanine transaminase (ALT) or aspartate transferase (AST) above the upper limit of normal (ULN) at both screening and baseline visits
11. Total bilirubin > 1.5 × ULN, except for Gilbert's syndrome
12. Alkaline phosphatase > 2.5 × ULN
13. Diabetes with HbA1c >7%
14. Presence or history of hepatitis B or hepatitis C infection (HBsAg-positive or HCV-RNA positive)
15. Evidence of chronic liver disease
16. Organ or stem cell transplant recipient or awaiting transplantation
17. Participation in another current or previous gene transfer study
18. AAVrh.10 neutralizing antibody titer ≥ 1:5
19. Other significant laboratory abnormalities or medical condition that the investigator feels may compromise the subject's safety
20. Female who is pregnant or lactating
21. History of alcohol or drug abuse within the past 5 years
22. Any history of allergies that may prohibit study-specific investigations; e.g., allergy to medications used for bronchoscopy
23. Receiving an investigational medicinal product (IMP) or participating in another investigational study with an IMP within 3 months prior to consent
24. Cigarette smoking, or any other tobacco use, or use of e-cigarettes or other recreational inhalant within 1 year of the Screening Visit.
25. Transfusion with human blood- or plasma-derived products within 8 weeks before scheduled Day 0 (treatment administration)

Estimated Study Duration:	A participant's total study duration will be up to 15 months (up to 3 months screening period and 12 months post-treatment monitoring). Upon completion, the subject will be offered enrollment in a long-term follow-up study to further assess the safety and durability of gene expression.
Efficacy Assessments:	• Concentrations of plasma A1AT (total and M-type) [redacted]

Safety Assessments:	The safety and tolerability of ADVM-043 are to be assessed by determining the incidence, severity, and dose-relationship of adverse events; and changes in the laboratory and other safety parameters (eg, vital signs, ECG, [redacted], etc.) by dose. The severity of AEs will be rated according to the CTCAE version 4.03. A Data Monitoring Committee (DMC) will be monitoring the safety of all subjects that have been administered ADVM-043.
Study Drug, Dosage, and Route of Administration:	Part A (intravenous infusion) Cohort 1: ADVM-043 at 8×10^{13} vg (1×10^{12} vg/kg based on an 80 kg subject) Cohort 2: ADVM-043 at 4×10^{14} vg (5×10^{12} vg/kg based on an 80 kg subject) Cohort 3: ADVM-043 at 1.2×10^{15} vg (1.5×10^{13} vg/kg based on an 80 kg subject) Cohort 4: ADVM-043 at 4.8×10^{15} vg (6×10^{13} vg/kg based on an 80 kg subject) Part B (intrapleural injection) Safety and efficacy data, including MTD, from Part A will be considered when determining whether to proceed to Part B
Statistical Methods:	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 [redacted] analyses are to be performed on all data collected in this study to gain further insight into the efficacy and safety of this gene therapy.
Date of Protocol:	30 Oct 2018

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List of Abbreviations

Abbreviation	Definition
A1AT	alpha-1 antitrypsin
AST	aspartate aminotransferase
BAL	bronchial alveolar lavage
cDNA	complementary DNA
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ELF	epithelial lining fluid
[redacted]	[redacted]
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

OTC	over-the-counter
PAT	protein augmentation therapy
[redacted]	[redacted]
PI	Principal Investigator
SAE	serious adverse event
SRM	Study Reference Manual
ULN	upper limit of normal
vg	vector genomes

1.0 INTRODUCTION

Clinical Protocol No. ADVM-043-01 is a Phase 1/2, first-in-human study to test the safety and efficacy of ADVM-043 in subjects with alpha-1 antitrypsin deficiency. It is designed as an open-label, multicenter, dose-escalation study to evaluate the safety and protein expression of ADVM-043 by 2 routes of administration: in Part A, a single dose is to be administered by intravenous (IV) infusion to a limited number of subjects. Based on the safety and efficacy data from Part A, the study may proceed to Part B. This decision will be made in consultation with the Study Primary Investigator. 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.

ADVM-043 is an investigational gene-therapy product that is intended to deliver a functional gene to the liver of patients with alpha-1 antitrypsin (A1AT) deficiency. These patients possess a mutation in the human A1AT gene that affects the production and normal functioning of A1AT protein, normally synthesized in the liver and secreted systemically. 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. In many patients with A1AT deficiency, insufficient anti-neutrophil elastase activity results in early-onset emphysema.

1.1 A1AT Deficiency

A1AT deficiency is a good target for gene therapy because it is a monogenic disorder. Therefore, in theory, gene replacement could benefit patients. In addition, A1AT protein levels can be readily measured in blood. Lastly, there is a wide therapeutic range for A1AT levels.

A1AT is a major inhibitor of serine proteases and plays an important role in the lung as an inhibitor of neutrophil elastase (NE), which cleaves numerous extracellular matrix proteins (Carrell and Lomas 2002; Stoller and Aboussouan 2005; Lungarella, Cavarra et al. 2008). An autosomal codominant disorder resulting in A1AT deficiency is associated with emphysema, and, in some individuals, liver disease (Brantly, Nukiwa et al. 1988; Hubbard and Crystal 1988; Crystal, Brantly et al. 1989; Crystal 1990; Lomas and Parfrey 2004; Greene, Miller et al. 2008; Silverman and Sandhaus 2009; Tuder, Janciauskiene et al. 2010). The most common form of A1AT deficiency is homozygous inheritance of the pathogenic Z allele (lysine replacing glutamic acid 342 in the functional M allele). In these patients, instead of producing the normally functioning M protein, the mutated Z protein is made. This designation is based on electrophoretic variants of A1AT proteins that have been identified, of which the M protein is the most common, and the Z protein is associated with the greatest risk for lung disease. The Z-A1AT protein tends to aggregate with other Z proteins, leading to intrahepatic polymerization of the mutant A1AT that results in reduced secretion, and, in turn, reduced serum A1AT levels (Nukiwa, Satoh et al. 1986; Curiel, Holmes et al. 1989; Brantly, Wittes et al. 1991; Lomas, Evans et al. 1992; Carrell and Lomas 2002; Lomas and Parfrey 2004). Normal human A1AT (M-A1AT) levels range from 1.09 to 2.61 mg/mL (~20 to 50 µM). Persons who carry the Z mutation in both alleles (ZZ genotype) typically have A1AT levels well below 0.57 mg/mL

(equivalent to 11 µM). A1AT deficiency resulting in 5-fold or greater decreases in plasma A1AT levels is associated with a greater risk for developing emphysema, COPD, bronchiectasis, and asthma. Much of the lung damage is thought to be caused by proteolytic damage from neutrophil elastase and other proteases (Brantly, Nukiwa et al. 1988; Hubbard and Crystal 1988; Crystal, Brantly et al. 1989; Crystal 1990; Greene, Miller et al. 2008; Tuder, Janciauskiene et al. 2010).

The FDA-approved treatment for A1AT deficiency is protein augmentation therapy (PAT), consisting of weekly IV infusions at 60 mg/kg subject bodyweight of purified A1AT from pooled human plasma (Gadek, Fells et al. 1981; Turner 2013). PAT has a number of limitations, including the burden of weekly IV infusions. As a result, although not approved by FDA, the therapy is sometimes administered at twice or four times the weekly dose at biweekly or monthly intervals (Hubbard and Crystal 1988; Hubbard and Crystal 1990; Dirksen, Dijkman et al. 1999; Zamora, Pla et al. 2008). As with any plasma-derived product, there is a theoretical risk of allergic reactions; viral or prion contamination; and supply limitations (Thompson Healthcare 2010, Stoller and Aboussouan 2012). Treating A1AT deficiency by gene therapy would offer several clinical advantages, including one single-dose administration; lower risk of infection or contamination; potentially lower risk of systemic allergic reactions; and fewer limitations in supply.

1.2 Prior Gene Therapy Studies in A1AT Deficiency

Although initial efforts to treat A1AT deficiency with gene therapy utilized various methods, such as recombinant adenoviral vectors, cationic liposome vector delivery, retroviral vectors, and naked DNA injection, delivery of a human A1AT gene via an AAV vector has progressed the furthest. Flotte and colleagues (Flotte, Trapnell et al. 2011) pioneered the use of AAV vectors in A1AT deficient patients, first using AAV2 in a Phase 1 trial and subsequently AAV1 in a Phase 1 and a Phase 2 trial to deliver the human A1AT cDNA via the intramuscular route. Although the AAV1 vector in the Phase 2 study resulted in persistent detectable vector-derived A1AT in serum and demonstrated a linear serum A1AT dose-response relationship, mean values in the highest dose cohort were 240 nM by Day 90, which is ≤ 3% of the target level of 11 µM likely to reduce the progression of disease (Flotte, Trapnell et al. 2011). Moreover, the high-dose cohort from the Flotte study required each subject to undergo 100 intramuscular injections to reach the target dose.

While the obvious route of administration of gene transfer therapies to the lung is via the respiratory epithelium, this route presents several barriers to successful gene transfer, including the respiratory epithelial fluid; the deficiency of viral receptors on the respiratory epithelial apical surface; and the anti-viral respiratory epithelial inflammatory/immune defenses (Yang, Li et al. 1995; Ferrari, Griesenbach et al. 2003).

In Clinical Protocol No. ADVM-043-01, intravenous and intrapleural routes of administration are being explored. In prior and ongoing hemophilia A and hemophilia B gene-therapy trials, gene transfer employing intravenously administered AAV vectors targeting the liver have resulted in significant increases in protein expression. Because the liver is the main secretory

organ responsible for the production of the A1AT protein, AAV-mediated gene transfer into liver cells holds clinical promise. One concern about increasing A1AT expression in liver cells is that non-functional A1AT protein aggregates may have caused liver damage and increasing A1AT production could worsen it. In this study, only patients without evidence of liver disease or detectable viral infection will be enrolled. Additionally, this study may pursue an alternative delivery method of ADVM-043 directly into the intrapleural space, as this approach potentially results in direct A1AT expression in the lung.

1.3 ADVM-043 Preclinical Evaluation

A 3-month Good Laboratory Practice (GLP) toxicology study was conducted to assess the safety, biodistribution, immunogenicity, and transgene expression profiles of the ADVM-043 drug product [redacted] Refer to Section 5.1 for the description of the investigational drug product.

Male and female mice were administered with a single IV infusion or intrapleural injection of vehicle or ADVM-043 with one of 2 doses at either 2×10^{11} vg/mouse (~1×10^{13} vg/kg) or 2×10^{12} vg/mouse (~1×10^{14} vg/kg). Human A1AT protein levels in the serum reached or exceeded the targeted therapeutic threshold in all dose groups except in female mice dosed with the ADVM-043 low dose (2×10^{11} vg/mouse or ~1×10^{13} vg/kg). This gender difference has been previously observed and may not hold true in larger animals (Lonning, Ford et al. 2002; Paneda, Lopez-Franco et al. 2013). [redacted]

[redacted]

Data obtained from the 3-month safety report [redacted] The 3-month safety data support the administration of ADVM-043 at the intended doses to study subjects enrolled in Clinical Protocol No. ADVM-043-01.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To assess the safety of ADVM-043 following intravenous administration

2.1.2 Secondary Objectives

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

2.2 Endpoints

2.2.1 Safety Endpoints

- Type, frequency, severity, duration, and relationship to study drug of any AEs and laboratory abnormalities graded according to CTCAE version 4.03

2.2.2 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]

A decision on whether to analyze novel biomarkers in serum is to be made after review of all efficacy and safety data and other emerging information, if any.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

Clinical Protocol No. ADVM-043-01 is a Phase 1/2, open-label, multicenter, dose-escalation clinical trial to evaluate the safety and treatment effect of ADVM-043, an IMP, in subjects with A1AT deficiency. The study is intended to test the hypothesis that administration of ADVM-043 (AAVrh.10 vector expressing human A1AT) 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 are to be treatment-naïve to PAT or to have stopped receiving PAT at least 8 weeks prior to treatment administration (Section 4.1). Therefore, detection of plasma A1AT levels over baseline will provide evidence of activity of ADVM-043.

In Part A, ADVM-043 is to be administered by intravenous (IV) infusion. In Part B, ADVM-043 is to be administered by intrapleural injection. Up to 4 dose-levels are to be tested in Part A (see below) and 1 dose-level in Part B. Safety and efficacy data, including maximum tolerated dose (MTD), from Part A will be considered when determining whether to proceed to Part B and the dose-level to be delivered.

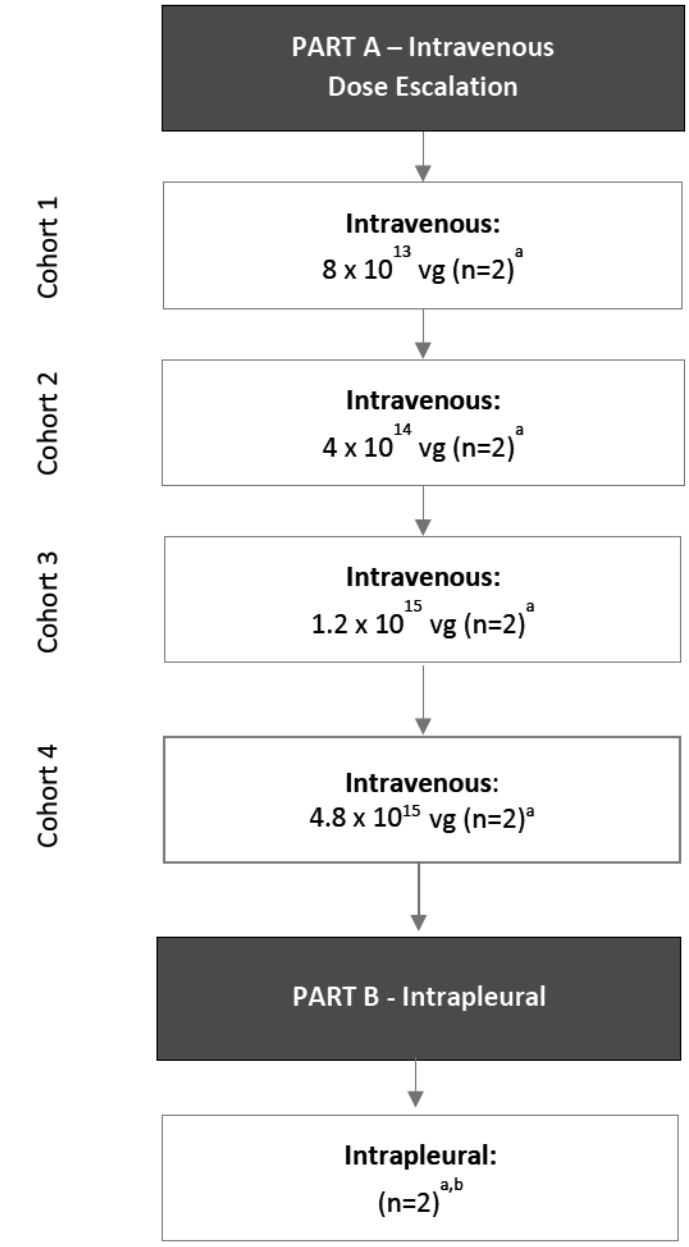
Cohort 1 ADVM-043 at 8×10^{13} vg
($\sim 1 \times 10^{12}$ vg/kg based on an 80-kg subject)

Cohort 2 ADVM-043 at 4×10^{14} vg
($\sim 5 \times 10^{12}$ vg/kg based on an 80-kg subject)

Cohort 3 ADVM-043 at 1.2×10^{15} vg
($\sim 1.5 \times 10^{13}$ vg/kg based on an 80-kg subject)

Cohort 4 ADVM-043 at 4.8×10^{15} vg |
($\sim 6 \times 10^{13}$ vg/kg based on an 80-kg subject)

Figure 1: Study Schema



a. There is the potential to expand each cohort by up to 3 subjects to total 5 subjects/Cohort
b. Data from Part A will be considered when determining dose for Part B

In addition to the ADVM-043 study treatment, [redacted]

Study visits and assessments over 52 weeks post-study treatment will permit monitoring of subject safety and change in A1AT concentration. Upon completion of the End-of-Study Visit (EOS), subjects will be offered enrollment in a long-term follow-up study to further assess the safety and durability of transgene expression.

A Data Monitoring Committee (DMC) will be involved in the study to ensure subject safety. Review of subject safety, including dose-limiting toxicities, will be conducted by the DMC and Adverum before potential dose-escalation to the next treatment cohort. Furthermore, specific safety signals may result in immediate suspension of further dosing and recruitment until a discussion and review of the safety data with the DMC has occurred (Section 3.10).

Adverum has every intention of completing Clinical Protocol No. ADVM-043-01. However, study activities can be terminated at any time, at the Sponsor's discretion.

3.2 Subject Population

The study population is to be limited to subjects with the ZZ or Z-Null A1AT genotype and a low baseline plasma concentration of A1AT. See Section 4.1 for the entry criteria. The total number of subjects to be treated is expected to be between 2 and 25.

Prospective subjects receiving PAT for A1AT deficiency-related lung disease must forego this treatment for at least 8 weeks prior to treatment dosing to support an adequate wash-out, plus a minimum of 3 months post-study treatment. Time off of PAT (at least 5 months) is not expected to have lasting adverse effects based on discussions with A1AT specialists. Furthermore, data from the A1AT Deficiency Registry Group comparing A1AT deficient patients who never received augmentation versus those who received augmentation showed that patients who received PAT at any time had similar benefits as those who were on PAT continuously (Alpha-1 Registry 1998). In Clinical Protocol No. ADVM-043-01, exogenous protein augmentation could confound measurement of plasma A1AT levels after ADVM-043 treatment. Regardless, at any time after treatment administration, the Investigator, in consultation with the Medical Monitor, may make a determination based on clinical judgment and study data to resume or start PAT. 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.

3.3 Cohort Size Rationale

The initial cohort size of 2 subjects is to minimize 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. Furthermore, A1AT deficiency is a rare disease, with a prevalence of about 1 to 5 per 10,000 (NLM 2018). This small population 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. In addition, data from historical clinical trials conducted in A1AT subjects support a low rate of withdrawal from the studies

(Chapman, Burdon et al. 2015), which further supports the initial cohort size of 2 subjects because the likelihood of subjects with incomplete data is predicted to be low.

Treatment-related adverse events (AE) are anticipated to be rare. Other studies investigating liver-directed gene therapies have reported mostly mild AEs, the majority of which were transient asymptomatic transaminitis. [redacted] an alanine aminotransferase (ALT) measurement of >2 × upper limit of normal (ULN) will trigger further clinical investigations (Section 13.2). These results will be reviewed closely by Adverum and are to be part of the cumulative safety data review by the DMC prior to a dose-escalation decision.

3.4 Cohort Assignment

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 is to be monitored for safety and treatment effects at protocol-specified study visits. 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 subject within a cohort. There will be a minimum of 4 weeks between dosing of the last subject in one dosing cohort and the first subject in the next dosing cohort which will include a DMC review of the safety and (as appropriate) efficacy data within a dosing cohort.

3.5 Rationale for dose selection

In Part A, ADVM-043 will be administered IV at 4 dose levels:

ADVM-043 at 8×10^{13} vg

ADVM-043 at 4×10^{14} vg

ADVM-043 at 1.2×10^{15} vg

ADVM-043 at 4.8×10^{15} vg

[redacted]

All 4 dose levels for Cohorts 1 through 4 remain below the NOAEL and are expected to be safe, based on the findings from Study ADVM-1701.

To date, over 100 clinical trials utilizing AAV driven gene therapy have been conducted (https://www.wiley.com/legacy/wileychi/genmed/clinical/). Multiple studies have used or are using similar doses to those being explored in this study. In one such study, doses up to 5.0×10^{12} vg/kg of liver-directed gene transfer for hemophilia B employing the AAVrh.10 vector (AAVrh.10FIX) were found to be generally well tolerated. (Dimension Therapeutics 2017). In a separate hemophilia A study conducted by BioMarin, the dosing of AAV5 (BMN 270) at 6×10^{13} vg/kg (approximately 4.6×10^{15} vg/subject based on the median weight) in 7 subjects has been shown to be safe and well-tolerated, and to produce durable and therapeutic FVIII levels out to 78 weeks (Biomarin 2017). BioMarin is currently conducting a global Phase 3 study in up to 40 subjects with hemophilia A with BMN 270 at 6×10^{13} vg/kg (ClinicalTrials.gov: NCT03370913 2018).

In ADVM-043-01, four dose levels have been selected to find a safe dose with the potential to show a meaningful effect in achieving plasma A1AT concentrations at or above the therapeutic target of 0.57 mg/mL (approximately 11 µM) that could potentially benefit patients with progressive lung disease. At the same time, we want to minimize patient exposure to sub-therapeutic doses of ADVM-043 and therefore have selected as low as 2 subjects per cohort (Section 3.3). Normal human A1AT (M-A1AT) levels range from 1.09 to 2.61 mg/mL (20 to 50 µM). [redacted] A starting clinical dose of [redacted] is projected to result in protein expression levels of approximately 0.04 to 0.1 mg/mL of M-A1AT in humans and that the highest dose of [redacted] may potentially reach approximately 2.4 to 6.0 mg/mL of M-A1AT in humans if the protein expression between mice and humans was equivalent.

Prior gene therapy studies have shown marked reduction in protein expression levels by four-fold or greater when comparing preclinical mouse studies to human trials (Bunting 2018; Nathwani, Rosales, et al 2011). As such, the primary objective of Cohort 1 is to establish an acceptable safety profile before proceeding to Cohorts 2 through Cohort 4. Given that AAVrh.10 and AAV8 have similar properties (both belong to Clade E family and differ by only 8% in their amino acid sequence (Wang, Bell, et al 2015), based on the protein expression results published by Nathwani employing AAV8, a 10-fold difference in expression may be reasonably predicted from mouse to human. If so, then the dose proposed in Cohort 4 may achieve up to ~0.6 mg/mL (~11 µM) protein expression, which would overlap with the minimum target therapeutic levels of total A1AT protein for patients with A1AT deficiency.

The Sponsor and the DMC will be reviewing the ongoing safety and protein expression data (as appropriate) from each Cohort prior to making the decision to dose escalate to the next dose level cohort.

[redacted]

3.6 Dose-Limiting Toxicity and Maximum Tolerated Dose

The first treated subject in a Cohort will be considered the sentinel subject. The proposed dosing interval is at least 14 days between the sentinel and second subject to be dosed, provided there are no safety concerns in the sentinel subject prior to dosing the next subject.

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 is based on data from ongoing studies in liver-targeting gene therapy showing that treatment-related adverse events have occurred in general within 4 weeks of study treatment and have not led to long term sequelae (Pasi 2017, Dimension Therapeutics 2017).

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. The DLT observation period will be used during the review between the DMC and Adverum to make decisions related to dose escalation and cohort expansion. If a subject

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

Any AE Grade ≥3 attributed to ADVM-043 that occurs outside of the DLT observation period will require enrollment suspension until review and assessment of the event has taken place (Section 3.9).

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 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.

3.7 Dose-escalation and cohort expansion criteria

As stated previously, 2 subjects will be treated in each dosing cohort and after the second subject has reached 4 weeks post-treatment, the DMC and Sponsor will review safety data for both subjects, because the DLT observation window will have passed for both subjects. Dose-escalation will not occur if there is a safety concern identified by the DMC or a DLT is reported (Section 3.6).

If a cohort is expanded beyond 2 subjects based on an identified DLT, 3 additional subjects will be dosed per cohort. Subject safety will be monitored on an ongoing basis by the Sponsor and Investigators. In addition, cohort review will be completed by the DMC when the last subject of the cohort has completed their DLT observation period. If only 1 DLT occurs in a total of 5 subjects within a dosing cohort, then the DMC and the Sponsor shall review all safety data and recommend dose escalation or progression to Part B.

If there are no DLTs in the 2 subjects dosed, dose escalation can proceed; ie, the next eligible subject will be enrolled in the next higher dosing cohort. An interval of at least 14 days will be required between the dosing of the sentinel and second subject in the next cohort.

If there are no DLTs observed in the first 2 subjects, the Sponsor may elect to expand the cohort to further evaluate safety or efficacy endpoints.

For dose-escalation decisions after Cohort 1, each time a second subject in a Cohort has reached at least 4 weeks post-treatment, the DMC and Sponsor will review safety data for both subjects in the cohort as well as the cumulative safety data of all treated subjects.

3.8 Progression to Part B

Safety and efficacy data from Part A will be considered when determining whether to proceed to Part B and the dose to be administered. Trough A1AT concentration > 11 µM (0.57 mg/mL) in serum has been established as the therapeutic threshold for PAT targeting lung disease secondary to A1AT deficiency. Therefore, if significant increase in A1AT concentration is not observed in Part A, Study Part B may not be pursued.

Part B is to include a single Cohort (n = 2 to 5 subjects). Dosing will be similar to Part A, with treatment of successive subjects separated by a similar observation period. Subjects in Part B will undergo bronchoscopy and bronchial alveolar lavage (BAL) for analysis of A1AT concentrations in ELF.

3.9 [redacted]

Asymptomatic hepatic transaminase elevations after vector administration were observed in early clinical studies with AAV-mediated gene transfer to subjects with moderate to severe hemophilia B (Manno, Pierce et al. 2006; Nathwani, Tuddenham et al. 2011; Nathwani, Reiss et al. 2014). In all cases, the transient rise in alanine aminotransferase (ALT) resolved without clinical sequelae; however, significant decline in transgene expression resulted.

It has been proposed that the transaminitis was a result of destruction of transduced hepatocytes after proliferation of anti-AAV capsid-specific memory CD8+ T cells upon vector antigen presentation via major histocompatibility complex class I (MHC I) pathways (Mingozzi and High 2013). This cell-mediated response is probably the result of a re-activation of anti-AAV capsid existing memory T cells, as there is widespread exposure in humans to AAV (Mingozzi, Maus et al. 2007). There is evidence that a short course of immunosuppression may attenuate the immune response (Manno, Pierce et al. 2006; Mingozzi, Hasbrouck et al. 2007; Mingozzi and High 2007).

[redacted]

[redacted]

Hepatic transaminase levels, specifically ALT and AST, will be monitored regularly throughout the study. Blood draws will be collected twice weekly from Day 1 post-treatment until [redacted]. Due to the potential variability of peak rise of transaminases based on prior studies, additional testing of ALT, AST, and other analytes may occur more frequently [redacted]. See schedule of assessments (SOA, Section 13.1) for detailed blood draw schedule.

[redacted], in the event of ALT >1.5 × ULN (or at a lower threshold at the discretion of the Investigator), the Investigator should contact the Medical Monitor to [redacted] In the event that the ALT does not return to baseline levels, further discussion between the Sponsor and the Investigator should occur to determine the appropriate treatment options.

Additionally, a significant decrease in M-type A1AT in the absence of elevated transaminases may be an early marker of immune response to transduced cells; therefore, [redacted]

[redacted]

To monitor for hepatotoxicity [redacted] clinical investigation for alternative causes of liver function abnormalities are to be performed if the ALT rises to > 2 × ULN.

[redacted]

[redacted]

3.10 Criteria for Suspension of the Clinical Study

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)

Any event that meets any suspension criterion is to be reported immediately to Adverum and ultimately to the appropriate regulatory authorities. Enrollment and dosing will be temporarily suspended until the risk to the subject is mitigated. The DMC will meet on an ad hoc basis to review and assess the event and it will be the responsibility of the DMC to make a recommendation to the Sponsor if they believe that enrollment should be suspended. The regulatory authorities and the Investigators, and each site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and other appropriate institutional regulatory bodies will be promptly notified by the Sponsor, if a decision to suspend enrollment is made. If enrollment is suspended, all treated subjects will continue to be monitored through their completion or withdrawal.

4.0 SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1 Selection of the Study Population

A sufficient number of subjects are to be screened to enroll between 2 and 25 subjects at approximately 5 clinical trial sites in the United States.

4.1.1 Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1) Capable of providing informed consent
2) Males and females ≥18 years of age
3) A1AT genotype ZZ or Z Null. Genotyping does not need to be performed for subjects for whom documented evidence of genotype from a qualified diagnostic lab is provided.
4) Plasma A1AT level <11 µM prior to the Baseline Visit

5) Any subject receiving A1AT protein augmentation therapy (PAT) must be willing to washout. Washout is defined as at least 8 weeks between last PAT dose and pre-treatment, plasma A1AT level.
6) Willing to remain off PAT for at least 3 months following treatment (Day 0)
7) Body mass index of 18 to 35 kg/m^2
8) Men and women of childbearing potential should agree to use barrier contraception for 3 months after treatment (Day 0).
9) Willing to participate in all study procedures and attend scheduled study visits

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria are to be excluded.

1) Forced expiratory volume in 1 second (FEV1) < 35 percent of predicted value at the Screening visit
2) Receiving systemic corticosteroids or other immunosuppressive medications
3) Immunodeficiency disease or evidence of active infection of any type, including human immunodeficiency virus
4) Evidence of major central nervous system, major psychiatric, musculoskeletal, or immune disorder
5) History of myocardial infarction within the past 1 year
6) History of cancer within the past 5 years, other than treated nonmelanomatous carcinoma of the skin and treated carcinoma in situ (CIS) of the cervix
7) Any clinically relevant abnormality evidenced by the screening hepatic ultrasound and/or chest x-ray
8) Within 24 hours of study treatment administration, evidence of active infection deemed clinically significant by the Investigator based on clinical exam and/or temperature > 38.5°C
9) Creatinine > 2 mg/dL.
10) Alanine transaminase (ALT) or aspartate transferase (AST) above the upper limit of normal at the Screening and the Baseline visits.
11) Total bilirubin > 1.5 × ULN, except for Gilbert's syndrome
12) Alkaline phosphatase > 2.5 × ULN
13) Diabetes with HbA1c >7%
14) Presence or history of hepatitis B or hepatitis C infection (HBsAg-positive or HCV-RNA positive)
15) Evidence of chronic liver disease

16) Organ or stem cell transplant recipient or awaiting transplantation

17) Participation in another current or previous gene transfer study

18) AAVrh.10 neutralizing antibody titer ≥ 1:5

19) Other significant laboratory abnormalities or medical condition that the investigator feels may compromise the subject's safety

20) Female who is pregnant or lactating

21) History of alcohol or drug abuse within the past 5 years

22) Any history of allergies that may prohibit study-specific investigations; e.g., allergy to medications used for bronchoscopy

23) Receiving an investigational medicinal product (IMP) or participating in another investigational study with an IMP within 3 months prior to consent

24) Cigarette smoking, or any other tobacco use, or use of e-cigarettes or other recreational inhalant within 1 year of the Screening Visit.

25) Transfusion with human blood- or plasma-derived products within 8 weeks before scheduled Day 0 (treatment administration)

4.2 Reasons for withdrawal/discontinuation

Subjects 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 trial site. Should a subject withdraw from the study, the Investigator should ensure that the subject's clinical care is continued. Every effort should be made to retain a subject in the study in order to monitor their safety.

Should a subject withdraw their consent for specific assessments (eg, bronchoscopy, imaging, [redacted], blood sampling), a protocol deviation should be recorded. All other assessments should be completed as specified by the protocol.

The reason for a subject not completing the study should be recorded. A subject may be withdrawn from the study for any of the following reasons:

26) Subject does not meet the eligibility criteria at the Baseline Visit

27) Lost to follow-up

28) Withdrawal of consent for participation in the study

29) Adverse event(s) that put the safety of the subject at risk

30) Major protocol deviation prior to treatment. The Investigator should discuss the protocol deviation with the Medical Monitor before withdrawing the subject

31) Investigator decides to discontinue the subject.

32) Sponsor decides to discontinue the subject.

33) Other (eg, death, inability to attend scheduled clinic visits, investigational medicinal product not administered).

The Investigator is to withdraw a subject if Adverum terminates the study.

4.3 Management of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the Investigator or at the request of Adverum.

When a subject withdraws from the study, the reason(s) for withdrawal are to be recorded on the electronic case report form (eCRF). Whenever possible, all subjects who withdraw from the study following treatment are to be encouraged to undergo all End-of-Study (EOS) assessments (Week 52 visit) (Section 6.4.16). The subject will be offered enrollment in a long-term follow-up study.

A subject who fails to return for EOS assessment is to be contacted by a representative from the clinical trial site in an attempt to have them complete protocol-specified assessments. Appropriate contact includes 2 documented phone calls followed by a registered letter before a subject may be listed as lost to follow up.

It is vital to obtain follow-up data on any subject who is withdrawn from the study and has an ongoing AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

4.4 Replacements

In the event that a subject withdraws prior to completion of the DLT observation window, the subject will be replaced and followed for DLT before decisions regarding subject replacement are made.

5.0 STUDY TREATMENTS

5.1 Formulation

The biological product 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). ADVM-043 is [redacted] Refer to the Investigator's Brochure for additional product details.

Investigational Drug Product

Product Name	ADVM-043	
Dosage Form	[redacted]	
Unit Dose	Part A	
	Cohort 1	ADVM-043 IV at 8×10^{13} vg
	Cohort 2	ADVM-043 IV at 4×10^{14} vg
	Cohort 3	ADVM-043 IV at 1.2×10^{15} vg
	Cohort 4	ADVM-043 IV at 4.8×10^{15} vg
	Part B	
	Dose for intrapleural injection will be determined from Part A	
Route(s) of Administration	Part A intravenous infusion	
	Part B intrapleural injection	
Physical Description	Once thawed, ADVM-043 is a clear, colorless liquid	

5.1.1 Study Drug Product Packaging and Labelling

ADVM-043 is supplied in ready-to-[redacted] and placed in an outer carton that displays the clinical label. The packaging and labeling operations are performed in a current Good Manufacturing Practice (cGMP) facility. The content of the labeling is in accordance with the local regulatory specification and requirements.

5.1.2 Study Drug Storage

ADVM-043 must be stored at [redacted].

5.1.3 Other Supplies

Clinical supplies required for the IV or intrapleural administration of IMP may either be sourced by clinical trial sites or provided by Adverum.

5.2 Product Accountability

The investigator is to maintain accurate records of receipt of ADVM-043, including dates of receipt.

Accurate records are to be kept regarding when and how much ADVM-043 has been administered to each subject. Reasons for departure from the expected administration regimen must be recorded.

5.3 ADVM-043 Dose Preparation and Administration

Refer to instructions for dose preparation and administration in the IMP Manual.

The IMP preparation for administration should be handled only by qualified clinical or pharmacy staff trained on the specific requirements of ADVM-043 preparation and administration procedures as outlined in the IMP Manual.

5.4 Prior, Concomitant, and Subsequent Therapy

5.4.1 Concomitant Medications

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

Use of any concomitant medications and any change in the use of concomitant medications are to be recorded by the investigator or designee in the eCRF. Any concomitant medication deemed necessary for the welfare of the subject may be given at the discretion of the Investigator.

5.4.2 Protein Augmentation Therapy

By Inclusion Criterion 5, a subject receiving PAT at or prior to Screening is to discontinue this therapy at least 8 weeks prior to Day 0 (treatment administration).

After the Week 12 visit, the treating physician in consultation with the Medical Monitor may make a determination 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 (ie, clinical laboratory tests, LFTs, [redacted] and assessment of AEs) according to the schedule of assessments.

[redacted]

[redacted]

5.4.4 Contraception

Women of childbearing potential and fertile men should utilize barrier birth control measures between Day 0 (treatment administration) and the Week 12 Visit.

5.4.5 Prohibited Concomitant Medications

There are no specific prohibited concomitant medications besides protein augmentation therapy. However, to reduce the likelihood of drug-drug interaction [redacted], the Investigator should discuss with Adverum any concomitant medication started after ADVM-043 treatment. During the study, any other investigational therapies, including ones to treat A1AT deficiency are, of course, prohibited.

6.0 STUDY ASSESSMENTS AND PROCEDURES

A prospective subject is required to sign an approved ICF before any study assessments and procedures are performed, including screening procedures and procedures to acquire baseline data or PAT washout, if needed. The Schedule of Assessments is displayed in tabular form in Section 13.1.

6.1 Efficacy Assessments

Blood and lung ELF samples should be collected, processed, and shipped using the methods described in the Study Reference Manual (SRM).

6.1.1 Plasma A1AT concentration, phenotype, and function

Concentrations of A1AT (total and M-type) will be measured [redacted]
Protein phenotype is to be determined [redacted] function is to be determined by assessment of [redacted]

[redacted]

6.1.2 Bronchoscopy and ELF collection (Part B subject only)

Bronchoscopy is to be conducted according to standard guidelines, as discussed in the SRM. All Investigators must be skilled operators for bronchoscopy.

6.1.3 Lung ELF A1AT concentration, phenotype, and function (Part B subject only)

Concentrations of lung ELF A1AT (total and M-type) are to be quantified [redacted]

Protein phenotype will be determined [redacted].

6.2 Safety Assessments

6.2.1 Physical examination

Physical examination (PE) is to evaluate the major body systems in order to identify any clinically significant disease or abnormality that, in the opinion of the Principal Investigator (PI), would exclude a subject from the study or preclude further study participation. A full PE is to 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 is to include examination of the skin and respiratory, cardiovascular, and gastrointestinal systems.

The subject is to undergo a full or abbreviated PE at visits shown on the Schedule of Assessments (Section 13.1).

6.2.2 Vital signs

Vital signs are to be obtained after the subject has rested in the sitting position for at least 5 minutes. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate and oral body temperature.

6.2.3 Height and weight

Height and weight will be recorded at the Screening visit. Additionally, weight will be measured at Weeks 24 and 52.

6.2.4 Clinical laboratory assessments

Clinical laboratory parameters to be measured are listed in Clinical Laboratory Assessments (Section 13.3). The procedures for collection and shipment are described in the Laboratory Manual.

Abnormal laboratory results must be evaluated as clinically significant or not clinically significant by the Investigator.

6.2.5 Pregnancy testing

Pregnancy testing is to be performed for women of child-bearing potential. Serum pregnancy test will be done at the Screening visit; and urine pregnancy test will be done at the Baseline and Week 52 visits. A positive result should be confirmed.

A woman with a positive pregnancy test should not undergo further invasive or contraindicated assessments, such as bronchoscopy and x-ray but may remain on study for routine assessments and follow-up.

6.2.6 12-lead electrocardiogram (ECG)

A 12-lead ECG measurement is to 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. ECGs are to be evaluated for clinically significant abnormalities, including [redacted] All attempts should be made to use the same ECG recorder for all subjects and throughout the study.

6.2.7 Chest imaging

Routine posterior-anterior chest x-ray is to be performed to assess the extent of pulmonary disease, to identify potential contraindications for intrapleural injection, and to assess the development and resolution of pneumothorax. All attempts should be made to use the same equipment for all subjects and throughout the study.

6.2.8 Hepatic ultrasound

A routine hepatic ultrasound is to be performed to assess the liver. All attempts should be made to use the same equipment for all subjects and throughout the study.

[redacted]

[redacted] are to be performed with validated and standardized machines. The procedures are to follow [redacted] as described in the SRM. All attempts should be made to use the same [redacted] equipment for all subjects and throughout the study.

6.3 Other Laboratory Assessments

6.3.1 Genotyping

Genotyping is to be performed [redacted]. The procedures for collection and shipment are described in the SRM. Genotyping is not necessary for a subject with documented evidence of genotype.

[redacted]

[redacted]. The procedures for collection and shipment of samples are described in the SRM.

[redacted]

[redacted] The procedures for collection and shipment of samples are described in the SRM.

[redacted]

[redacted] The procedures for sample collection and shipment are described in the SRM.

[redacted]

[redacted]

6.4 Study Visits

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 rescreened upon consultation with Adverum.

6.4.1 Screening Visit (≤3 months before Day 0)

The following procedures are to be completed at the Screening Visit:

- Informed consent
- Medical history
- Demographic information
- Review of inclusion/exclusion criteria
- Physical examination (PE)
- Height and weight for BMI
- Vital signs
- 12-lead ECG

[redacted]

- Blood sample for total A1AT level (For a subject who had received PAT prior to Screening, this sampling must be performed 8 weeks or more after discontinuation of PAT.)
- Clinical laboratory assessments

[redacted]

[redacted]

- Serum pregnancy

[redacted]

- Chest x-ray (posterior-anterior)
- Hepatic ultrasound

[redacted]

- AE review (study procedures related only)
- Concomitant medications
- Bronchoscopy and lung ELF sample for total A1AT level (Part B subject only)

6.4.2 Baseline Visit (Prior to Study Treatment)

Any subject meeting all entry criteria at Screening is to be scheduled for the Baseline Visit. Assessments for Baseline Visit may be done at the local lab anytime within 36 hours of study treatment administration (Day 0), however ALT/AST must be confirmed within the normal range and urine pregnancy test must be negative prior to dosing. The following procedures are to be performed:

- Review of inclusion/exclusion criteria
- PE
- Vital signs
- Central laboratory assessments

[redacted]

- Local laboratory assessments
  - AST and ALT

[redacted]

- Blood sample for A1AT levels and function

[redacted]

[redacted]

- Concomitant medications
- AEs (study procedures related only)

6.4.3 Treatment Visit (Day 0)

The subject is to be admitted to the clinical trial site or clinical research unit for treatment administration and overnight safety monitoring.

6.4.3.1 Pre-treatment procedures:

[redacted]

- Vital signs
- Review local laboratory baseline AST/ALT and urine pregnancy results

6.4.3.2 ADVM-043 administration

The ADVM-043 dose is to be prepared and administered according to the instructions in the IMP Manual.

6.4.3.3 Post treatment procedures

- Vital signs
- Safety monitoring: hourly (±15 minutes) until 6 hours post-treatment; then every 2 hours (±15 minutes) until 12 hours post-treatment; then every 4 hours (±15 minutes) until time of discharge. Observation is to be for safety and to determine whether any immediate toxicity is or may be attributable to ADVM-043. The subject will be discharged from the clinical research unit approximately 24 hours after the completion of the treatment procedure.

6.4.4 Day 1 Visit

- Abbreviated PE
- Vital signs

[redacted]

- Clinical laboratory assessments

[redacted]

[redacted]

- Concomitant medications
- AEs

The subject will be discharged only if there are no new clinically significant findings, AEs, or laboratory abnormalities that may be attributable to ADVM-043.

6.4.5 Day 2 Visit

- Vital signs

[redacted]

- Clinical laboratory assessments

[redacted]

- Concomitant medications
- AEs

6.4.6 Day 3 Visit

- Vital signs

[redacted]

- Concomitant medications
- AEs

6.4.7 Day 7 Visit (±1 day)

- Abbreviated PE
  - Vital signs

[redacted]

  - Schedule outpatient ALT/AST blood draws
  - Clinical laboratory assessments

[redacted]

- Blood sample for A1AT levels and function
- Concomitant medications
- AEs

6.4.8 Post-treatment LFTs (ALT/AST) Assessment

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

For those timepoints that occurred outside of a scheduled visit, the blood draw can be conducted by a contracted home-based medical personnel.

6.4.9 Day 14 Visit (±1 day)

- Blood sample for ALT and AST
- Blood sample for A1AT levels and function
- Concomitant medications
- AEs

6.4.10 Day 21 (±2 days)

- Blood sample for ALT and AST
- Blood sample for A1AT levels and function

6.4.11 Week 4 Visit (±2 days)

- Abbreviated PE
- Vital signs
- Clinical laboratory assessments
- Bronchoscopy and lung ELF sample (Part B subjects only)

[redacted]

- Blood sample for A1AT levels and function

[redacted]

- Concomitant medications
- AEs

6.4.12 Post-treatment A1AT Levels [redacted]

A1AT levels and functions will be assessed at Day 7, 14, 21 and Weeks 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 40 and 52.

For those timepoints that occur outside of a scheduled visit, the blood draw can be conducted by a contracted home-based medical personnel. For subjects who resume or start PAT post-treatment, A1AT levels do not need to be obtained.

6.4.13 Week 8 Visit (±2 days)

- Abbreviated PE
- Vital signs
- Blood sample for ALT and AST
- Blood sample for A1AT levels and function

[redacted]

- Concomitant medications
- AEs

6.4.14 Week 12 (±5 days)

- Abbreviated PE
- Vital signs

[redacted]

- Blood sample for A1AT levels and function

[redacted] (Section 3.9; Table 2)

- Clinical laboratory assessments

[redacted]

- Concomitant medications
- AEs

6.4.15 Week 24 (±7 days)

- Abbreviated PE
- Vital signs
- Weight

[redacted]

- Blood sample for A1AT levels and function

[redacted]

- Clinical laboratory assessments

[redacted]

- Bronchoscopy and lung ELF sample (Part B subjects only)

[redacted]

- Concomitant medications
- AEs

6.4.16 Week 52, End of Study (EOS) or Early Withdrawal Visit (±14 days)

- PE
- Vital signs
- Weight
- 12 lead ECG
- Blood sample for A1AT levels and function

[redacted]

- Clinical laboratory assessments

[redacted]

- Urine pregnancy

[redacted]

- Concomitant medications
- AEs

Upon completion, the subject is to be offered enrollment into a long-term follow-up study.

6.4.17 Unscheduled Visit

- Vital signs
- Concomitant medications
- AEs

Any other assessments are to be performed at the discretion of the Investigator.

7.0 ASSESSMENT OF SAFETY

The Investigator or site staff is to be responsible for detecting, documenting, and reporting all events that meet the definition of an AE or an SAE, regardless of relationship to ADVM-043 or their clinical significance.

For AEs and SAEs, the reporting period begins at the time a subject signs the informed consent and ends at 30 days after the last study visit. Between the time of informed consent and study treatment administration, only AEs (non serious and serious) assessed as related to study procedures should be reported. After treatment administration (Day 0), all AEs (serious and non serious, related and unrelated) should be reported.

Unless a subject withdraws consent for follow-up, each subject must be followed until a) the end of the AE reporting period at 30 days after the last study visit or
b) any ongoing drug-related AEs and SAEs have resolved or become stable. The Investigator should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The Adverum medical monitor may request that certain SAE/AEs be followed longer.

An SAE that is observed or reported prior to treatment administration and is associated with protocol-mandated interventions (eg, medication washout, bronchoscopy, or BAL) is to be recorded on the eCRF.

Any abnormal laboratory test result (hematology, chemistry, coagulation, or urinalysis) or other safety assessments (ECG, chest x-ray, vital sign measurements), is to be recorded as an AE or SAE. This includes those that worsen from Baseline and are clinically significant in the medical and scientific judgment of the Investigator,.

However, any clinically significant safety assessment that is associated with the underlying disease is not to be reported as an AE or SAE, unless judged by the Investigator to be more severe than expected for the subject's condition.

7.1 Definitions of Adverse Events

7.1.1 Definition of adverse event

An adverse event (AE) is any untoward medical occurrence in an enrolled subject regardless of its causal relationship to the IMP.

7.1.2 Definition of Treatment-Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is any event not present before exposure to the IMP or any event already present that worsens in either intensity or frequency after exposure to the IMP. The subject is to be instructed to contact the Investigator at any time after treatment administration if any symptoms develop.

7.1.3 Definition of Serious Adverse Event

A serious adverse event (SAE) is 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 inpatient 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias; or convulsions that do not result in inpatient hospitalization; and the development of drug dependency or drug abuse.

7.1.4 Definition of Treatment-Emergent Serious Adverse Event

A treatment-emergent serious adverse event is an event meeting the definition of SAE and not present before exposure to the IMP; or any event already present that worsens in either intensity or frequency after exposure to the IMP.

7.1.5 Definition of Pregnancy-Related Event

Pregnancy is not regarded as an AE unless there is a suspicion that an IMP may have interfered with the effectiveness of a contraceptive medication.

To ensure subject safety, any pregnancy must be recorded on a clinical study pregnancy form; the form must be sent to Adverum within 2 weeks of the study visit during which the pregnancy was reported. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject withdrew.

Any pregnancy complication and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriage must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the subject has completed the study, and considered by the Investigator as possibly related to the study treatment must be promptly reported to Adverum.

7.2 Eliciting and Documenting Adverse Events

At every study visit, the subject is to be asked a standard non-leading question to elicit any medically related changes in their well-being; and if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription and OTC). AEs identified from any study data (laboratory values, PE findings, ECG changes) or from review of other documents relevant to subject safety are to be documented on the AE page in the eCRF.

7.3 Reporting Adverse Events

All AEs reported or observed during the study are to be recorded on the AE eCRF. Information to be collected includes event term, time of onset; Investigator assessment of seriousness, severity, and relationship to ADVM-043; time of resolution of the event; any required treatment or evaluations; and outcome. An AE resulting from concurrent illnesses, reactions to concurrent

illnesses, reactions to concurrent medications, or progression of disease states must be reported. All AEs are to be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be recorded as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any SAE must be reported to [redacted] immediately; ie, within 24 hours after the time site personnel first learn about the event. The following contact information is to be used for SAE reporting:

[redacted]

Prompt notification of SAEs by the Investigator to Adverum [redacted] is essential so that legal and ethical responsibilities towards the safety of subjects are met.

Adverum [redacted] has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of ADVM-043. Adverum [redacted] will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

Investigator safety reports are prepared for suspected unexpected SAEs according to local regulatory requirements and Adverum [redacted] policy and are forwarded to Investigators as necessary.

Any Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Adverum [redacted] is to file it with the IRB and notify the IRB/IEC, if appropriate according to local requirements.

7.3.1 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) version 4.0.

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.

7.3.2 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.

The relationship or association of ADVM-043 in causing or contributing to the AE is to be characterized using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study drug and the reported event.
Possible:	This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.
Probable:	This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.
Definite:	This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

7.4 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic, or not clinically significant, or until the subject is considered stable.

In the event that a subject dies while participating in the study, the Investigator should request a full autopsy to determine the precise cause of death. If possible, and if death is within 60 days of treatment administration, samples of tissues obtained at autopsy are to be evaluated for the presence of the AAV genome.

7.5 Data Monitoring Committee

A DMC is to be convened according to a DMC Charter established for this protocol. The DMC will consist of [redacted] The primary role of the committee is to provide an objective review of emerging safety data with Adverum to ensure that the safety of subjects is maintained. Additionally, the DMC is to review the safety and (as appropriate) efficacy data, and make recommendations regarding the safety of dose-escalation, and dose cohort expansion in Part A as well as progression to Study Part B.

7.6 Overdose

An overdose is any dose of study treatment given to or taken by a subject that exceeds the dose described in the protocol.

7.6.1 Overdose reporting

Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor. An overdose without signs or symptoms is not to be recorded as an AE; any AEs associated with the overdose is to be reported on the eCRF.

7.6.2 Treatment of overdose

There is no specific antidote for overdose of ADVM-043. In the event of a suspected overdose, it is recommended that supportive clinical care be instituted as considered appropriate by the investigator, based on the subject's clinical symptoms.

8.0 STATISTICAL METHODS

Study ADVM-043-01 is a Phase 1/2 safety and preliminary-measure-of-efficacy study. As a Phase 1/2 safety study, no formal statistical analysis is required. Descriptive and exploratory analyses are to be performed on all data to gain further insight into the efficacy and safety of this gene transfer therapy.

8.1 Analysis Set

The full analysis set (FAS) is to consist of all subjects who receive ADVM-043. The FAS will be used for presenting demographics, baseline characteristics, efficacy, and overall safety and tolerability assessments. Assessments will be grouped in cohorts and in aggregate.

8.2 Description of Subgroup Analysis

No subgroup analyses are planned.

8.3 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.2 or later. There is to be no formal statistical testing performed. All safety and efficacy variables are to be summarized descriptively. Continuous variables are to be summarized using the mean; the standard deviation; and median, minimum, and maximum value. Categorical variables are to be summarized using frequency counts and percentages. Data will be provided in data listings.

8.3.1 Safety analyses

AEs are to be coded using the MedDRA classification to give a preferred term (PT) and system organ class (SOC) for each event. Numbers and percentages of subjects with TEAEs will be presented. All AEs will be listed. Tables of TEAEs will be presented by SOC and PT. These tables are to include overall totals for AEs within each organ class. The number of subjects with an event in each classification of severity and relationship to treatment within each treatment cohort will be tabulated. SAEs and AEs leading to withdrawal from the study will be listed separately.

All other safety parameters will be summarized by cohort and aggregate. All safety data will be listed.

8.3.2 Efficacy analyses

Concentrations of total and M-type A1AT over time, [redacted] are to be summarized. Similar summaries are to be generated [redacted] Any analysis conducted on exploratory biomarker samples are to be summarized.

8.3.3 Other Analyses

Summary statistics are to be provided for demographics, medical history, physical examination, vital signs, ECG parameters, [redacted], and safety laboratory analyses [redacted]

8.3.4 Interim Analyses

No interim analyses are planned.

8.4 Data Quality Assurance

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Adverum is to conduct a quality assurance assessment or audit or both of the site records. FDA may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit, or inspection, the investigator and institution must agree to grant the advisors, auditors and inspectors direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings or relevant issues and to implement any corrective or preventive actions.

8.5 Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, spirometry and lung function reports, ECGs, etc.

Subject data are to be entered via an eCRF into Medidata Rave electronic data capture platform. Data provided from other sources will be received, reconciled, combined and transferred to Adverum Biotechnologies, Inc. at agreed-upon timepoints.

Management of clinical data will be performed in accordance with [redacted] to ensure the integrity of the data; ie, removing errors and inconsistencies in the data. AEs and concomitant medication terms are to be coded using MedDRA (Version 19.0) and the WHO Drug Dictionary, respectively.

The eCRFs (including queries and audit trails) will be sent at the end of the study in CD format to Adverum Biotechnologies, Inc. to be retained. Each Investigator is to receive a copy of their site-specific data in the same format to maintain as the Investigator copy. In all cases, subject initials will not be collected or transmitted.

9.0 ETHICS

9.1 Independent Ethics Committee / Institutional Review Board/ Institutional Biosafety Committee

Federal regulations and the International Council on Harmonisation (ICH) guidelines require that approval be obtained from an Institutional Review Board / Institutional Biosafety Committee (IRB / IBC) before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, 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 IRB / IBC. Documentation of all IRB / IBC approvals and of the IRB / IBC compliance with ICH Harmonised Tripartite Guideline E6: Good Clinical Practice (GCP) will be maintained by the site and will be available for review by Adverum or its designee.

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

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 IRB / IBC. The Investigator must promptly supply Adverum or its designee, the IRB / IBC, and, where applicable, the institution, with written reports of any changes significantly affecting the conduct of the study or increasing the risk to subjects.

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 ICH Harmonised Tripartite Guideline E6: Good Clinical Practice; 21CFR; and applicable laws and regulations.

9.3 Subject Information and Consent

A study-specific informed consent form (ICF) in compliance with US Title 21 CFR Part 50 is to be approved by Adverum, the PI, and the IRB. Each prospective subject or their legal guardian will be given a full explanation of the study and be allowed to read the approved ICF under conditions where there is adequate time to consider the risks and benefits associated with participation in the study. Once the PI is assured that the subject/legal guardian understands the implications of participating in the study, and before any unusual or nonroutine procedure that involves risk to the subject, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF. The investigator must also sign the ICF. The investigator shall retain the signed original ICF and give a copy of the signed original form to the subject or legal guardian.

The PI or delegate shall maintain a log of all subjects or their representatives who sign the ICF and indicate whether the subject was enrolled or reason for nonenrollment.

An ICF template may be provided by Adverum to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the revised ICF should be reviewed by Adverum or its designee or both before IRB submission. Once reviewed, the ICF is to be submitted by the PI to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all actively participating subjects must sign the revised form.

10.0 INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or legal guardian, except as necessary for monitoring and auditing by Adverum, its designee, regulatory authorities, or the IRB.

The Investigator and all employees and coworkers involved with this study must not disclose or use for any purpose other than conduct of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Adverum or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Adverum to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. The investigator must provide to Adverum a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

[redacted]

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E68.2 and Title 21 of the CFR by providing to Adverum, the following essential documents, including but not limited to:

- IRB approval
- Signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae (CV) for the PI and each Sub-investigator listed on FDA Form 1572
- Financial disclosure information to allow Adverum to submit complete and accurate certification or disclosure statements required under 21 CFR 54. The Investigators must provide to Adverum a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

- IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study the Investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. The investigator agrees to submit annual reports to the study site IRB as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB with a summary of the study outcome and Adverum and regulatory authority(ies) with any reports required.

10.8 Records Retention

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 [redacted] have elapsed since the formal discontinuation of clinical development of ADVM-043. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Adverum. It is the responsibility of Adverum to inform the Investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, Adverum will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it is to be submitted, and other related issues. Adverum has final approval authority over all such issues.

Data are the property of Adverum and cannot be published without prior authorization from Adverum; but data and publication thereof will not be unduly withheld.

11.0 STUDY MANAGEMENT

11.1 Monitoring

11.1.1 Monitoring of the Study

The clinical monitor, as a representative of Adverum, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

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

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow Adverum, representatives of Adverum, or a regulatory agency such as FDA access to all study records.

The Investigator should promptly notify Adverum [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports to Adverum.

11.2 Management of Protocol Amendments and Deviations

11.2.1 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 Adverum or designee. Protocol Amendments must be submitted to the Investigator's IRB for approval before any subject can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A protocol deviation is any unintended or unanticipated departure from the procedures and processes as specified in the protocol. A significant protocol deviation occurs when there is nonadherence to the protocol by the subject or Investigator that results in a significant additional risk to the subject. 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. Any protocol deviation will lead to the subject being withdrawn from the study (Section 4.2).

The Investigator or designee must document and explain in the subject's source documentation any protocol deviation. The Investigator may implement a deviation from the protocol to eliminate an immediate hazard to a study subject without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to Adverum for agreement, and to the regulatory authorities, if required.

Protocol deviations are to be documented by the clinical monitor throughout the course of monitoring visits. PIs are to be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Adverum Biotechnologies, Inc., has every intention of completing the study. However, Adverum is authorized to terminate the study at any time for clinical or administrative reasons.

11.4 Final Report

Whether the study is completed or prematurely terminated, Adverum will ensure that the clinical study reports (CSR) are prepared and provided to the regulatory agencies as required. Adverum will also ensure that the CSR in marketing applications meet the standards of the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports.

Where indicated by regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator is to be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, Adverum is to provide the investigator with the summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

12.0 REFERENCE LIST

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13.0 APPENDICES

13.1 Schedule of Assessments ADVM-043-01 Protocol Amendment 7 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]						[redacted]				[redacted]
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																							
[redacted]	[redacted]	[redacted]					[redacted]			[redacted]				[redacted]						[redacted]				[redacted]

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]						[redacted]				[redacted]
[redacted]		[redacted]					[redacted]			[redacted]				[redacted]						[redacted]				[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]	[redacted]																			[redacted]				[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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]						[redacted]				[redacted]
[redacted]		[redacted]					[redacted]			[redacted]				[redacted]						[redacted]				[redacted]
[redacted]		[redacted]					[redacted]			[redacted]				[redacted]						[redacted]				[redacted]
[redacted]		[redacted]		[redacted]	[redacted]		[redacted]			[redacted]				[redacted]						[redacted]				[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]		[redacted]		[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 [redacted] 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 Blood 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

13.2 Appendix: Assessment & Management of Potential Acute Liver Injury

In the event a subject develops ALT > 2 × ULN, the study site will make every reasonable attempt to have the subject return to the clinic within 24 hours and conduct the following investigations:

Repeat liver function tests

Hepatitis A IgM

Hepatitis B surface antigen and hepatitis B core IgM

Hepatitis C RNA.

Cytomegalovirus IgM

Epstein-Barr viral capsid antigen IgM (if unavailable, obtain heterophile antibody or monospot testing)

Hepatitis E IgM

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)

Measure direct bilirubin if total bilirubin ≥2 × ULN

Measure INR

Full blood count including differential white cell count for eosinophilia

Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies

Liver imaging (magnetic resonance) to evaluate liver disease

If acetaminophen is a potential contributor, measure serum acetaminophen adduct HPLC assay if available locally

Record the appearance or worsening of clinical symptoms of hepatitis (jaundice, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the Adverse Events eCRF.

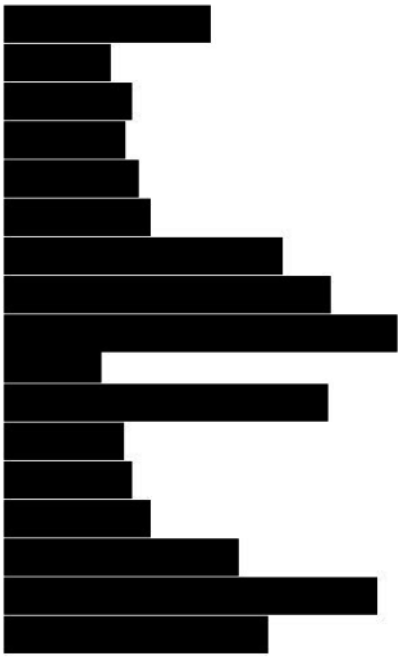
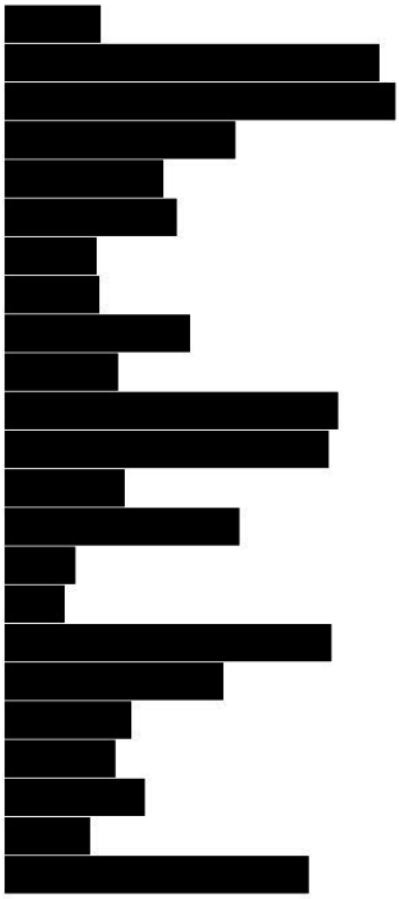
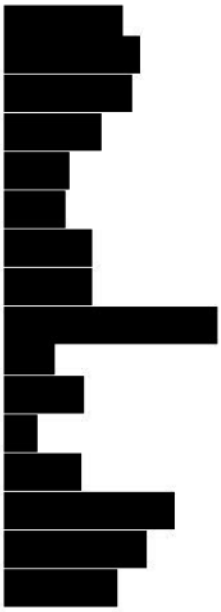
Record use of concomitant medications, acetaminophen, herbal remedies, other-over-the-counter medications, or putative hepatotoxins on the Concomitant Medications eCRF.

Record alcohol use.

Monitor subjects at least weekly until liver chemistries (ALT, AST, alkaline phosphatase, total and direct bilirubin) resolve, stabilize, or return to within baseline values.

13.3 Clinical Laboratory Assessments

Clinical Laboratory Assessments

Hematology	Chemistry	Urinalysis
		

Other	Coagulation
HIV 1/2	Prothrombin time
HBsAg Qualitative	Activated Partial Thromboplastin Time (APTT)
HCV-RNA Qualitative	Fibrinogen
	INR

* Iron, LDH and Mg will be performed as needed at the PI's discretion.