CLINICAL STUDY PROTOCOL

Study ID	ADVM-022-04
Study Title	A Phase 2, Multi-Center, Randomized, Double-Masked, Active Controlled Study of ADVM-022 (AAV.7m8-aflibercept) in Subjects with Diabetic Macular Edema [INFINITY]
Indication Studied	Diabetic Macular Edema (DME)
Sponsor	Adverum Biotechnologies, Inc. 800 Saginaw Drive Redwood City, CA 94063
Protocol Version	Document Identifier / Effective Date
Original	ADVM-022-04 / 19 March 2020
Amendment 1.0	ADVM-022-04 v1.0 / 16 April 2020
Amendment 2.0	ADVM-022-04 v2.0 / 04 May 2020
Amendment 3.0	ADVM-022-04 v3.0 / 02 September 2020
Amendment 4.0	ADVM-022-04 v4.0 / 17 February 2021
Amendment 5.0	ADVM-022-04 v5.0 / 04 May 2021
Amendment 6.0	ADVM-022-04 v6.0 / 14 July 2021
Amendment 7.0	ADVM-022-04 7.0 / 05 August 2021

INVESTIGATOR AGREEMENT

Study ID	ADVM-022-04
Study Title	A Phase 2, Multi-Center, Randomized, Double-Masked, Active Controlled, Study of ADVM-022 (AAV.7m8-aflibercept) in Subjects with Diabetic Macular Edema [INFINITY]
Version	Amendment 7.0, 05 August 2021

I have read this clinical protocol as set forth below. On behalf of myself and the study staff, I agree to conduct Study ADVM-022-04 in compliance with the terms of the protocol as outlined herein and in compliance with Good Clinical Practice (GCP) and all applicable legal and regulatory requirements. Furthermore, I understand that the Sponsor, Adverum Biotechnologies, Inc. (Adverum), and the Institutional Review Board/Institutional Biosafety Committee (IRB/IBC) must approve any changes to the protocol in writing before implementation, except where it may be necessary to eliminate an immediate hazard to a subject enrolled in this study. I agree not to divulge to anyone, either during or after the study, any confidential information acquired regarding the investigational medicinal product and processes or methods of Adverum. All data pertaining to this study will be provided to Adverum.

_____ _____

Principal Investigator (signature) Date

Printed Name:

Institution:

STUDY CONTACTS

Sponsor	Adverum Biotechnologies, Inc. 800 Saginaw Drive Redwood City, CA 94063
Sponsor's Medical Monitor	[redacted] Medical Director phone: [redacted] email: [redacted]
SAE Reporting	Phone: [redacted] Fax: [redacted] Email: [redacted]

PROTOCOL APPROVAL—ADVERUM SIGNATORY

Study ID	ADVM-022-04
Study Title	A Phase 2, Multi-Center, Randomized, Double-Masked, Active Controlled Study of ADVM-022 (AAV.7m8-aflibercept) in Subjects with Diabetic Macular Edema [INFINITY]
Version	Amendment 7.0, 05 August 2021

Study ADVM-022-04 will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Harmonised Tripartite Guidelines for Good Clinical Practices (E6), with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21, and the ethical principles outlined in the Declaration of Helsinki).

Protocol approved by:

[redacted]
Adverum Biotechnologies, Inc.

Signature [redacted] Date [redacted]

TABLE OF CONTENTS

LIST OF TABLES

1.0 STUDY SYNOPSIS

Title of Study:	A Phase 2, Multi-Center, Randomized, Double-Masked, Active Controlled Study of ADVM-022 (AAV.7m8-aflibercept) in Subjects with Diabetic Macular Edema [INFINITY]
Sponsor:	Adverum Biotechnologies, Inc.
Phase of Development:	Phase 2
Study Sites:	Approximately 15 sites in the United States
Objectives:	**Primary Objective:** • To assess the durability of a single intravitreal (IVT) injection of ADVM-022 **Secondary Objectives:** • To assess the safety and tolerability of ADVM-022 • To evaluate the effect of ADVM-022 on macular edema • To evaluate the effect of ADVM-022 on Best Corrected Visual Acuity (BCVA) • To evaluate the effect of ADVM-022 on Diabetic Retinopathy Severity Scale (DRSS) score • To assess the need for rescue aflibercept (2 mg IVT) • To assess the effect of a preceding dose of aflibercept (2 mg IVT) prior to ADVM-022 administration • To evaluate the effect of ADVM-022 on development of vision threatening complications (including anterior segment neovascularization, vitreous hemorrhage, or tractional retinal detachment)
Primary Endpoint:	• Time to worsening of DME disease activity in the study eye
Secondary Endpoints:	Unless specified otherwise, the secondary endpoints are based on outcome measures for the study eye. • Incidence and severity of ocular and non-ocular adverse events (AEs) • Change from Baseline in central subfield thickness (CST) and macular volume over time through Week 96 • Change from Baseline in BCVA over time through Week 96 • Frequency of rescue aflibercept (2 mg IVT) in the study eye over time during the study • Incidence of 2-step and 3-step improvement in DRSS score over time through Week 96

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

	• Incidence of 2-step and 3-step worsening in DRSS score over time through Week 96 • Occurrence of vision threatening complications (anterior segment neovascularization, vitreous hemorrhage, or any other high-risk proliferative DR or tractional retinal detachment) over time through Week 96 • Incidence of CST <300 μm over time through Week 96 • Incidence of clinically significant findings via physical examinations, ocular examinations, imaging, and laboratory evaluation
Investigational Product and Dosage:	ADVM-022 (AAV.7m8-aflibercept) investigational medicinal product is a genetically engineered, replication incompetent, capsid variant of the adeno-associated viral vector of serotype 2 (AAV2). A single 0.10 mL IVT administration of ADVM-022 will be evaluated at two dose levels: 2×10^{11} vg/eye and 6×10^{11} vg/eye.
Reference Therapy:	Name: Eylea® (aflibercept) Dosage, Route, Frequency: 0.05 mL of 2 mg administered via IVT for a single injection.
Study Design:	This is a multi-center, randomized, double-masked, controlled, parallel-group study to evaluate the efficacy, safety and tolerability of a single IVT injection of ADVM-022. Two doses of ADVM-022 will be investigated. Subjects with initial diagnosis of DME within 6 months of screening and have received up to 2 prior injections of anti-VEGF therapy are eligible for enrollment. Approximately 33 eligible subjects will be randomized to one of 5 arms. Arm 1 (n=6) will receive ADVM-022 6×10^{11} vg/eye with a preceding aflibercept dose. Arm 2 (n=6) will receive ADVM-022 6×10^{11} vg/eye of without a preceding aflibercept dose. Arm 3 (n=6) will receive ADVM-022 2×10^{11} vg/eye with a preceding aflibercept dose. Arm 4 (n=6) will receive ADVM-022 2×10^{11} vg/eye of without a preceding aflibercept dose. Arm 5 (n=9) will receive aflibercept only (active control). To maintain masking of the treatment assignment, subjects assigned to the arms with no preceding aflibercept on Day 1 or to the arm with no ADVM-022 on Day 8 will receive a sham ocular injection on the corresponding visit. Only one eye per subject will be selected as the study eye. If both eyes are eligible, the eye with the worse BCVA will be the study eye.

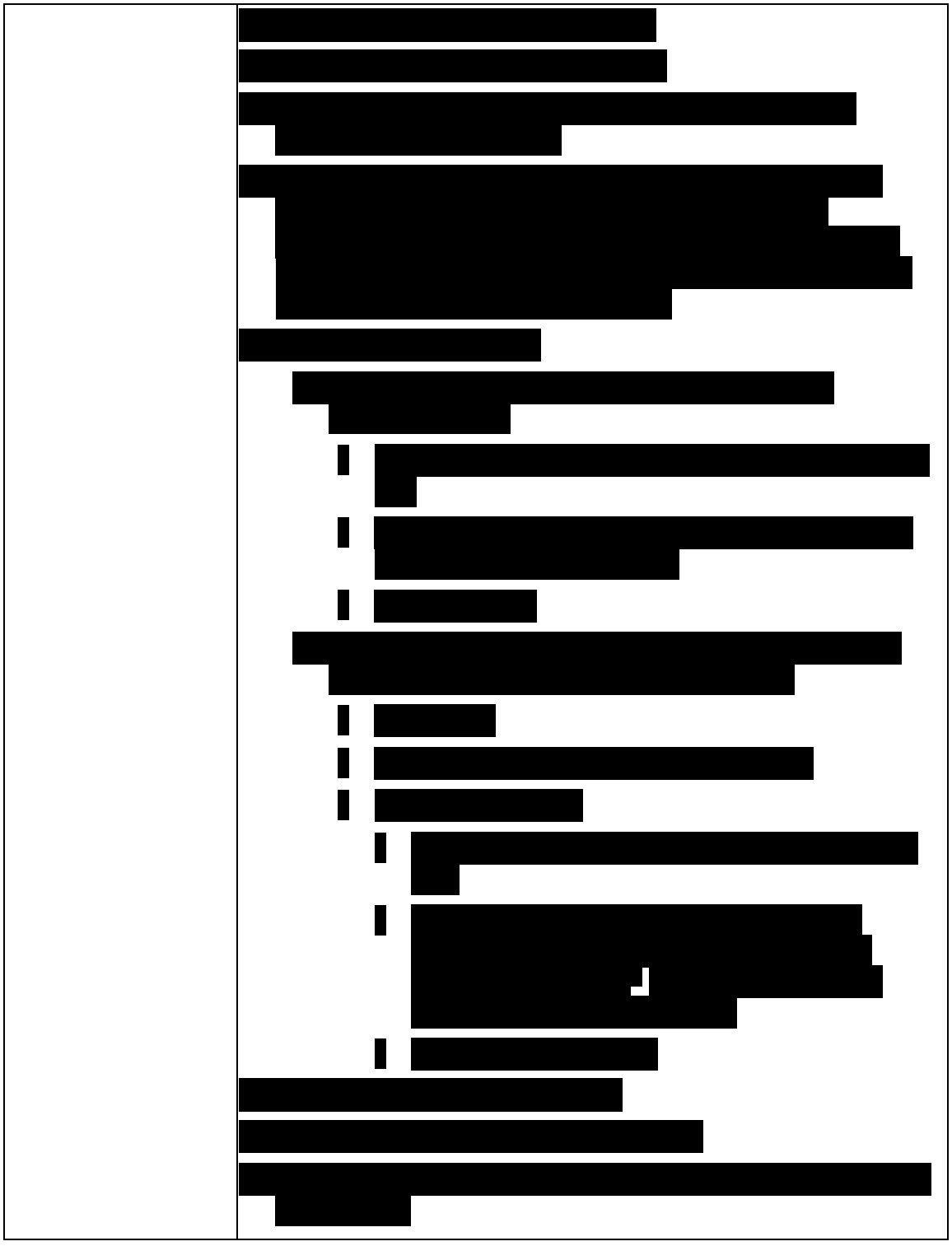
Subjects will be randomized to the following treatment arms in the following table:

Arm	N	Day 1 IVT Aflibercept or Sham	Day 8 IVT ADVM-022 Dose (vg/eye)
1	6	Aflibercept	6×10^{11}
2	6	Sham	6×10^{11}
3	6	Aflibercept	2×10^{11}
4	6	Sham	2×10^{11}
5	9	Aflibercept	Sham

After the assigned IVT injections on Day 1 and Day 8, all subjects will return to the clinic on Week 2, Week 4, and then every 4 weeks up to Week 96. To maintain masking, both subjects and the site personnel who conduct outcome assessments will be masked to the treatment assignment throughout the study. Emergency unmasking for all subjects may be required, as determined by the Sponsor with input from the Data Monitoring Committee, to preserve subject safety. In the event of unmasking of all subjects prior to the end of the study, the study will in effect become an open-label study, in which all prior masked roles will be able to continue study participation in an unmasked manner.

[redacted]

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**



Adverum Biotechnologies, Inc.
Clinical Protocol No. ADVM-022-04
ADVM-022 (AAV.7m8-aflibercept)
Amendment 7.0, 05 August 2021

[redacted]

Rescue Treatment:

Starting at Week 8, subjects will receive rescue aflibercept (2 mg IVT) if they meet any of the following:

- Increase in CST > 50 µm as assessed by SD-OCT compared to the lower of the two CST measurements recorded at Day 1 or Week 4
- Loss of > 5 letters in BCVA due to worsening DME disease activity compared to the higher of the two BCVA measurements recorded at Day 1 or Week 4.

After the initial rescue treatment administration, subsequent rescue treatment may be administered PRN per the discretion of the Primary Investigator.

Only intravitreal aflibercept injection (Eylea) is to be used for any rescue treatment unless prior approval by medical monitor.

Aflibercept should not be injected in eyes with active inflammation. A minimum of 21 days is required between rescue aflibercept injections.

Independent Data Monitoring Committee (DMC)

An independent DMC will monitor safety and study conduct on an ongoing basis. Members of the DMC will be independent from the Sponsor and will follow a charter that outlines the DMC's roles and responsibilities. The DMC will meet every 3-6 months (frequency adjustable as required) to evaluate unmasked ocular and non-ocular safety events, with emphasis on the evaluation of the rate of ocular inflammation, increased intraocular pressure (IOP), endophthalmitis, and clinically significant decreases in BCVA. The DMC will also meet on an ad hoc basis if stopping rules are met as outlined below. The DMC may recommend stopping the study early for safety reasons. After reviewing the data, the DMC will provide a recommendation to the Sponsor as described in the DMC Charter. Any outcomes of these data

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

	reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs). **Stopping Rules:** Enrollment will be suspended if any of the following sight threatening events occur: • A decrease of ≥ 30 letters in BCVA in the study eye compared with the prior visit • A surgical intervention (i.e., conventional surgery, vitrectomy) to prevent permanent loss of sight • Severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitreous cells) In addition, enrollment will be suspended if any serious adverse event potentially related to ADVM-022 occurs. Any event that meets any of the above safety stopping criteria will be reported immediately to the Sponsor and enrollment and dosing will be suspended until the DMC has reviewed the data and made a recommendation to the Sponsor. The regulatory authorities and the Investigators, and each site's IRB and other appropriate institutional regulatory bodies will be promptly notified 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.
Study Duration:	Duration of subject's participation in the study will be approximately 100 weeks for each subject (including up to 4-week screening period)
Number of Subjects:	Approximately 33 subjects
Study Population:	Subjects with newly diagnosed DME (diagnosis within 6 months of screening) that have received up to 2 prior injections of anti-VEGF therapy in the study eye.
Randomization Criteria:	Subjects must meet the following criteria to be included in this study:
Inclusion Criteria:	1) Male or female subjects, age ≥ 18 years of age 2) Type 1 or 2 diabetes mellitus 3) Ability and willingness to provide informed consent to participate in the study requirements and visits prior to any study procedure 4) Vision at Screening visit:

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

	a) Study Eye-BCVA 78 to 50 ETDRS letters, inclusive (approximate Snellen equivalent 20/32 to 20/100) b) Non-study eye-BCVA 35 ETDRS letters or more (approximate Snellen equivalent of 20/200 or better) 5) CST of study eye at Screening visit of ≥ 325µm using Heidelberg Spectralis® with center involving intraretinal fluid (IRF) 6) A decrease in vision in the study eye determined by the investigator to be primarily due to DME 7) Initial DME diagnosis within 6 months from screening 8) Up to 2 prior injections (0, 1 or 2) of anti-VEGF in the study eye • If a prior anti-VEGF has been administered to the study eye, in the judgement of the Investigator, there must have been a meaningful CST response (e.g., ≥ 10% reduction) and no adverse reaction to anti-VEGF (e.g., inflammation). 9) A minimum 60-day interval is required between the last anti-VEGF IVT injection in the study eye and randomization on Day 1
Exclusion Criteria:	Participants with any of the following conditions are ineligible: **General Exclusion Criteria** [redacted] 2) Any condition that, in the opinion of the investigator, could contraindicate the use of the investigational drug or that might affect interpretation of the study results or that renders the subject at high risk for treatment complications. 3) Received an investigational medicinal product within 60 days or 5 half-lives prior to dosing with ADVM-022, whichever is longer 4) Prior ocular gene therapy 5) History of allergy to aflibercept, corticosteroid, or fluorescein dye or sodium fluorescein used in angiography (mild allergy amenable to treatment is allowable) 6) Pregnancy a) Women who ever intend to become pregnant b) Women who are currently or ever intend to breastfeed c) For women of childbearing potential (a woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (>12 continuous months of

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

	amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of both ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements): i) May participate only if they have a negative pregnancy test at screening ii) Must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate < 1% per year (1) Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices. (2) Contraception methods that do not result in a failure rate of < 1% per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. 7) History or evidence of any of the following cardiovascular disease within 6 months of dosing: a) Severe cardiac disease (e.g., New York Heart Association [NYHA] Functional Class III or IV) or clinical evidence of unstable angina b) Acute coronary syndrome, myocardial infarction or coronary artery revascularization c) Ventricular tachyarrhythmias requiring ongoing treatment, or uncontrolled arrhythmia d) Uncontrolled hypertension defined as systolic blood pressure (SBP) >160 mmHg or a diastolic blood pressure (DBP) >100 mmHg, despite using BP–lowering medication within the screening period. If BP-lowering medications are required, subject should be on a stable dose of the same medication continuously for 30 days prior to randomization. e) History of cerebrovascular accident or transient ischemic attack 8) Any history of ongoing bleeding disorders. The use of aspirin or other anticoagulants (e.g., Factor Xa inhibitors) is not an exclusion.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

	9) HbA1C >10%; or history of diabetic ketoacidosis within 3 months prior to randomization; or subjects who, within the last 3 months, initiated intensive insulin treatment (a pump or multiple daily injection) or plan to do so in the next 3 months [redacted] 12) History of malignancy within the last 5 years except for the following adequately treated: a) Local basal cell or squamous cell carcinoma of the skin b) Carcinoma in situ of the cervix or breast c) Papillary, noninvasive bladder cancer d) Prostate cancer Stage 1 and 2 for which observation is clinically indicated with stable prostate-specific antigen (PSA) for 6 months e) Any other cancer that has been in complete remission for at least 2 years or considered surgically cured 13) Known to be positive for HIV or active viral hepatitis (unless documented cure after treatment for Hepatitis C) 14) Known history of syphilis 15) Known severe renal impairment, as indicated by estimated CrCl <30 mL/min (by Cockcroft-Gault calculation); need or anticipated need for hemodialysis during the study period 16) Other significant laboratory abnormalities that the Investigator feels may compromise the subject's safety 17) Any febrile illness within 1 week prior to randomization. **Ocular Exclusion Criteria (Study Eye)** 18) High-risk PDR at time of screening, defined as: any vitreous or preretinal hemorrhage, neovascularization elsewhere >1/2-disc area within an area equivalent to standard ETDRS 7-field on clinical examination, or neovascularization of disc > 1/3-disc area on clinical examination

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

	19) Any prior focal or grid laser photocoagulation or any prior PRP in the study eye [redacted] 23) History of retinal disease in the study eye other than diabetic retinopathy including age-related macular degeneration (in either eye), retinal vein occlusion, retinal arterial occlusion, pathologic myopia etc.) 24) Any current or history of ocular disease other than DME that, could reduce the potential for visual improvement, confound assessment of the macula or require medical or surgical intervention during the study (e.g. significant cataract, macular traction) or any evidence of posterior subcapsular cataract 25) History of cataract extraction or YAG capsulotomy within 3 months before Day 1 26) History of retinal detachment (with or without repair) in the study eye 27) History of trabeculectomy or glaucoma shunt or minimally invasive glaucoma surgery (MIGS) [redacted]

	[redacted] **Ocular Exclusion Criteria (Fellow or Study Eye)** [redacted] 36) Known history of ocular HSV, VZV, or CMV including viral uveitis, retinitis or keratitis 37) Evidence of external ocular infection, including conjunctivitis, chalazion or significant blepharitis 38) History of ocular toxoplasmosis
Minimization of Bias:	Subjects will be randomized to one of 5 arms. The treatment assignment will be masked to the subject, the physician and/or staff conducting outcome assessments, the central reading center and the sponsor. At the study site, only the site staff that prepares the study drug for administration and the physician administering the study drug will be unmasked. See the IMP manual for additional details. An independent review of OCT images, fluorescein angiography (FA) and fundus photographs, will be performed at a central reading center to provide an objective assessment of these evaluations. Safety and disease activity assessment will be performed by the masked physician. Unmasking of subject treatment assignments was planned to be reserved until the end of the study. Emergency unmasking for all subjects has been required, as determined by the Sponsor with input from the Data Monitoring Committee, to preserve subject safety. The study in effect has become an open-label study, in which all prior masked roles will be able to continue study participation in an unmasked manner.
Method of Administration:	Both ADVM-022 and aflibercept will be administered via IVT injection. Aseptic technique with povidone-iodine will be employed. Topical and/or subconjunctival anesthesia will also be used. Post-injection care and medication regimen will be given based as institutional standard of care. The sham ocular injection procedure will also be done under the same conditions but with an empty syringe without a needle (using the blunt end) pressed against the eye to mimic an injection.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Safety Assessments:	The safety of ADVM-022 will be assessed through the collection of AEs, vital signs, physical examinations, ocular examinations, imaging, and laboratory evaluations.
Statistical Methods and Data Analysis:	No formal statistical testing is planned for the study. All safety and efficacy variables will be summarized descriptively by treatment arm. Mean, standard deviation (SD), median and range will be provided for continuous variables; and frequency counts and percentages will be provided for categorical variables. Kaplan-Meier survival analysis will be utilized to derive median time to the first occurrence of DME disease worsening. All rescue aflibercept injections received by each subject during the study will be summarized using statistical models for recurrent events. Mean cumulative function (MCF) curve over time will be plotted for the mean cumulative number of injections. Mixed-effect models for repeated measures (MMRM) will be employed to explore the treatment effect on the change over time in BCVA and CST. The treatment effect on DRSS changes over time will be explored using generalized mixed models for categorical outcomes. Interim analysis is planned after all subjects have been followed 24 weeks. As unmasking of all subjects has occurred prior to the end of the study, the study in effect has become an open-label study.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

2.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AAV	Adeno-Associated Virus
AE	Adverse Event
AMD	Age-Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BID	Two times a day
cDNA	Complementary DNA
CBC	Complete blood count
CFR	Code of Federal Regulations
CIOMS	Council of International Organizations of Medical Sciences
CMV	Cytomegalovirus
CNV	Choroidal Neovascularization
CRF	Case Report Form
CrCl	Creatinine Clearance
CRO	Clinical Research Organization
CST	Central Subfield Thickness
CTA	Clinical Trial Agreement
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRSS	Diabetic Retinopathy Severity Scale
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic data capture
[redacted]	[redacted]
[redacted]	[redacted]
EOS	End of Study

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Abbreviation or Term	Definition/Explanation
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein Angiography
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HED	Human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act of 1996
HEENT	Head, ears, eyes, nose, and throat
HIV	Human Immunodeficiency Virus
HbA1c	Glycated hemoglobin
HSV	Herpes Simplex Virus
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
INR	International Normalized Ratio
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IUD	Intrauterine Device
IVT	Intravitreal
[redacted]	[redacted]
KPs	Keratic Precipitates
MCF	Mean cumulative function
MIGS	Minimally invasive glaucoma surgery
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Abbreviation or Term	Definition/Explanation
[redacted]	[redacted]
nAMD	Neovascular (wet) Age-Related Macular Degeneration
NSAID	Nonsteroidal anti-inflammatory drug
NHP	Nonhuman Primate
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
OTC	Over the counter
OU	Oculus Uterque (both eyes)
PASS	Power and Sample Size (a proprietary software)
PDR	Proliferative Diabetic Retinopathy
PE	Physical Examination
PRP	Pan Retinal Photocoagulation
PSA	Prostate-specific antigen
PT	Preferred term
Q2hr	Every 2 hours
QD	Once a day
QID	Four times a day
QoD	Once every other day
rAAV	Recombinant Adeno-Associated Virus
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Abbreviation or Term	Definition/Explanation
Sf9	Clonal isolate of *Spodoptera frugiperda* Sf21 commonly used in insect cells culture for recombinant protein production using baculovirus
sFLT-1	Soluble FLT-1 Receptor / Soluble VEGFR1 Receptor
SOC	System Organ Class
sVEGFR	Soluble Vascular Endothelial Growth Factor Receptor
TID	Three times a day
UBM	Ultrasound Biomicroscopy
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR1	Vascular Endothelial Growth Factor Receptor 1
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
VZV	Varicella-zoster virus
YAG	Yttrium Aluminum Garnet

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

3.0 BACKGROUND

3.1 Introduction

Diabetic Retinopathy (DR) is a major complication of diabetes mellitus (DM) and is a leading cause of visual loss in the working age population (Wang 2018). Diabetic Macular Edema (DME) is a complication of DR that affects central vision and can lead to a decline in vision ranging from slight visual blurring to blindness, substantially affecting independence and quality of life (Varma 2014). Anti-vascular endothelial growth factor (anti-VEGF) agents such as aflibercept (Eylea®), approved by the Food and Drug Administration (FDA), have demonstrated effectiveness at improving and maintaining vision in patients with DR and DME. However, patients with DR and DME can struggle to adhere to treatment regimens with Eylea that call for monthly or bimonthly intravitreal (IVT) injections often leading to suboptimal outcomes in the real world. This may be because diabetic patients are subject to significant lapses in follow-up because of illness, financial hardship or noncompliance. In patients treated with currently available anti-VEGF therapy alone, unintentional treatment interruptions can result in blinding complications including vitreous hemorrhage and tractional retinal detachment (Wubben 2019). There is, therefore, an unmet need for a long-acting anti-VEGF agent that can reduce the risks associated with lapses in follow-up.

Gene-based delivery of anti-VEGF proteins has the potential to provide sustained intraocular anti-VEGF protein expression following a single administration, addressing this unmet medical need. ADVM-022 is a gene therapy product that uses an adeno-associated viral vector capsid (AAV.7m8) encoding DNA for aflibercept and is administered as a single IVT injection. ADVM-022 is designed to provide sustained therapeutic levels of aflibercept and to minimize the burden of frequent anti-VEGF injections in the treatment of DME.

3.2 Investigational Medicinal Product (ADVM-022)

The investigational medicinal product (IMP), ADVM-022 (AAV.7m8-aflibercept), is a recombinant, replication-deficient adeno-associated viral (rAAV) vector containing the AAV.7m8 protein capsid derived by in-vivo directed evolution on the AAV2 capsid (Dalkara 2013). ADVM-022 carries an expression cassette of a codon-optimized version of the aflibercept complementary DNA (cDNA) under the control of a ubiquitous promoter. ADVM-022 is manufactured using the baculovirus expression vector system in Sf9 cells where two different baculoviruses are used, one encoding the genes for AAV2 Rep and AAV.7m8 Cap proteins, and the other encoding the human aflibercept cDNA expression cassette.

ADVM-022 offers the potential for sustained intraocular expression of aflibercept, an anti-VEGF protein following a single IVT administration, the same route of administration that is standard for anti-VEGF drugs currently administered to patients.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

3.3 Preclinical Summary for ADVM-022

Results from nonhuman primate (NHP) preclinical pharmacology studies of ADVM-022 conducted in a clinically relevant animal model of ocular neovascularization, laser-induced choroidal neovascularization (CNV), demonstrated the robust pharmacologic effects of ADVM-022 (Grishanin 2019). A single IVT injection of ADVM-022 administered 2 months or 13 months prior to laser photocoagulation reduced Grade IV lesion development to the same extent as a 1.2 mg IVT bolus of aflibercept recombinant protein (a current standard of care for nAMD and DR including DME) administered at the time of lesioning. The effect of ADVM-022 treatment on Grade IV CNV lesion incidence (as measured by FA) correlated with smaller size of fibrovascular CNV complexes (as measured by SD-OCT). Notably, the effects on CNV development were identical whether the lesions were induced 2 months or 13 months post-ADVM-022 administration, demonstrating the durability of the protective effect of this treatment.

Analysis of aflibercept levels demonstrates that IVT injection of ADVM-022 provides sustained intraocular expression that results in high levels of aflibercept in the tissue in which DR and nAMD, i.e., retina and choroid. Aflibercept levels found in the aqueous and vitreous humor, as well as ocular tissues of African green monkeys plateaued by one-month post-dose and were maintained out to 30 months post-administration, the last time point assessed (Johnston 2013). ADVM-022 administration was well-tolerated, showing transient intraocular inflammation that generally resolved over time. The preclinical pharmacology studies provide a strong demonstration of the potential efficacy of IVT-delivered ADVM-022.

3.4 Other Clinical Studies of ADVM-022

Clinical Protocol No. ADVM-022-01 (also referred to as the OPTIC study, ClinicalTrials.gov Identifier: NCT03748784) is a Phase 1, open-label, multi-center study to evaluate the safety and tolerability of a single IVT injection of ADVM-022 in subjects with nAMD. Secondary objectives include evaluating the effect of ADVM-022 on best corrected visual acuity (BCVA), central subfield thickness (CST), macular volume, the need for rescue therapy, and presence of subretinal or intraretinal fluid.

To be eligible for the study, subjects needed to be older than 50 years of age, have had prior or current evidence of active subfoveal CNV secondary to Age-Related Macular Degeneration (AMD), have received a minimum of 2 anti-VEGF injections within 4 months prior to screening, have vision in the study eye between 78 to 25 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters, have vision in the non-study eye of ≥ 35 ETDRS letters, have demonstrated a meaningful anti-VEGF response defined as a reduction from diagnosis in CST by 30% or a reduction from screening in CST by 20% or normalization of CST with no wet AMD activity. Eligible subjects enrolled in the first two cohorts (Cohorts 1 and 2) received a dose of ADVM-022 at 6×10^{11} vg/eye and 2×10^{11} vg/eye, respectively, with a prophylactic oral prednisone regimen. Cohorts 3 and 4 subjects received a dose of ADVM-022 at 2×10^{11} vg/eye and 6×10^{11} vg/eye, respectively, with a prophylactic topical difluprednate regimen.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

The OPTIC study is ongoing as of the data cut-off date for this submission of March 10, 2021, with the planned 4 cohorts fully enrolled [redacted] all of whom have been dosed with ADVM-022. Patients completing OPTIC are encouraged to enroll in an ongoing 3-year long-term extension study at the last study visit (104 weeks), with similar ongoing assessments, Clinical Protocol No. ADVM-022-07 [OPTIC-EXT] (ClinicalTrials.gov: NCT04645212), initiated in November 2020.

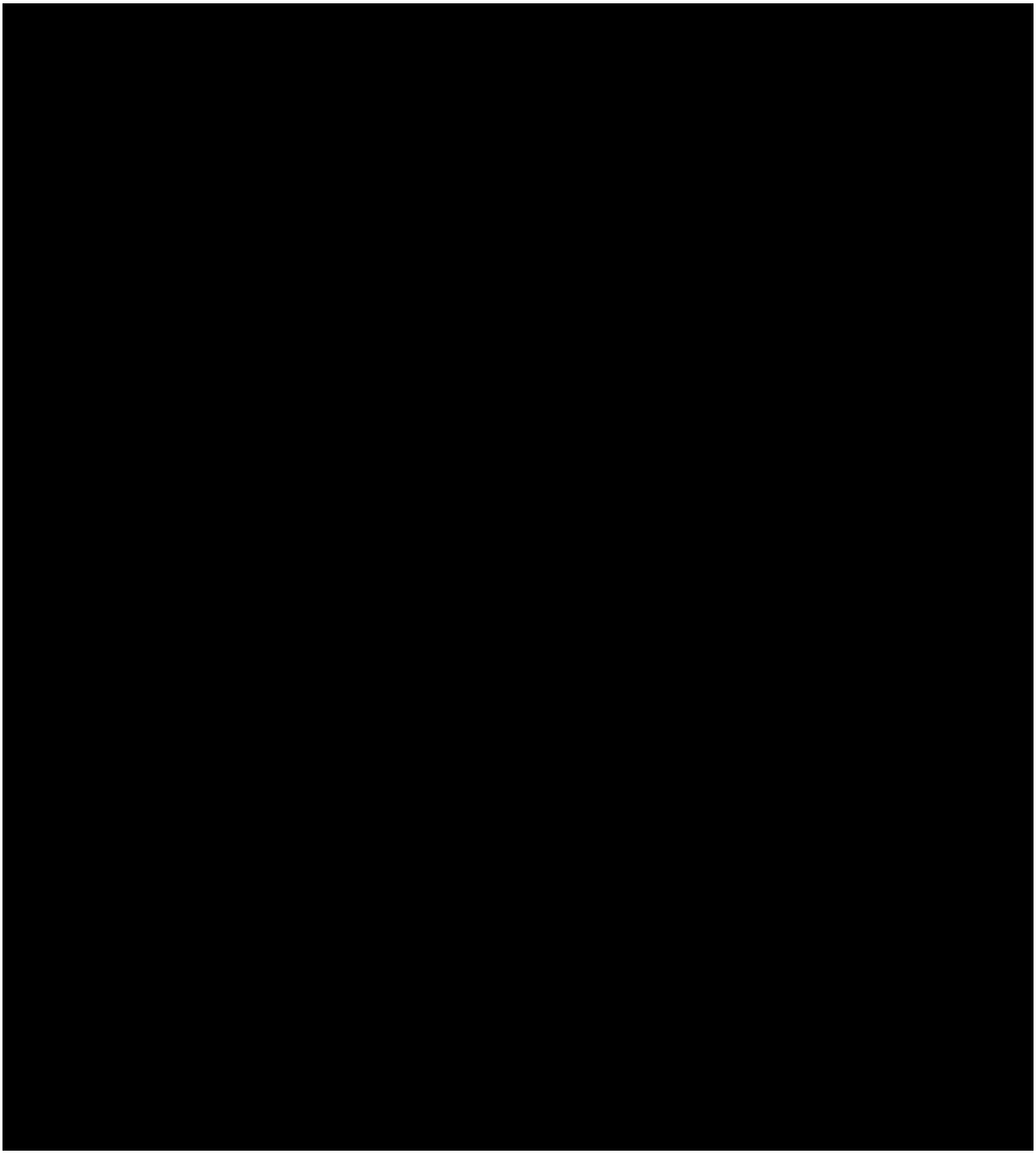
[redacted]

The OPTIC study population consisted of patients who previously required frequent injections to maintain vision. The mean years since diagnosis per cohort were 4.5 years, 4.1 years, 3.3 years, and 3.2 years for Cohorts 1-4 respectively. The mean number of anti-VEGF injections in the 12 months prior to receiving ADVM-022 were 9.2, 9.2, 9.1, and 7.1 in Cohorts 1-4 respectively.

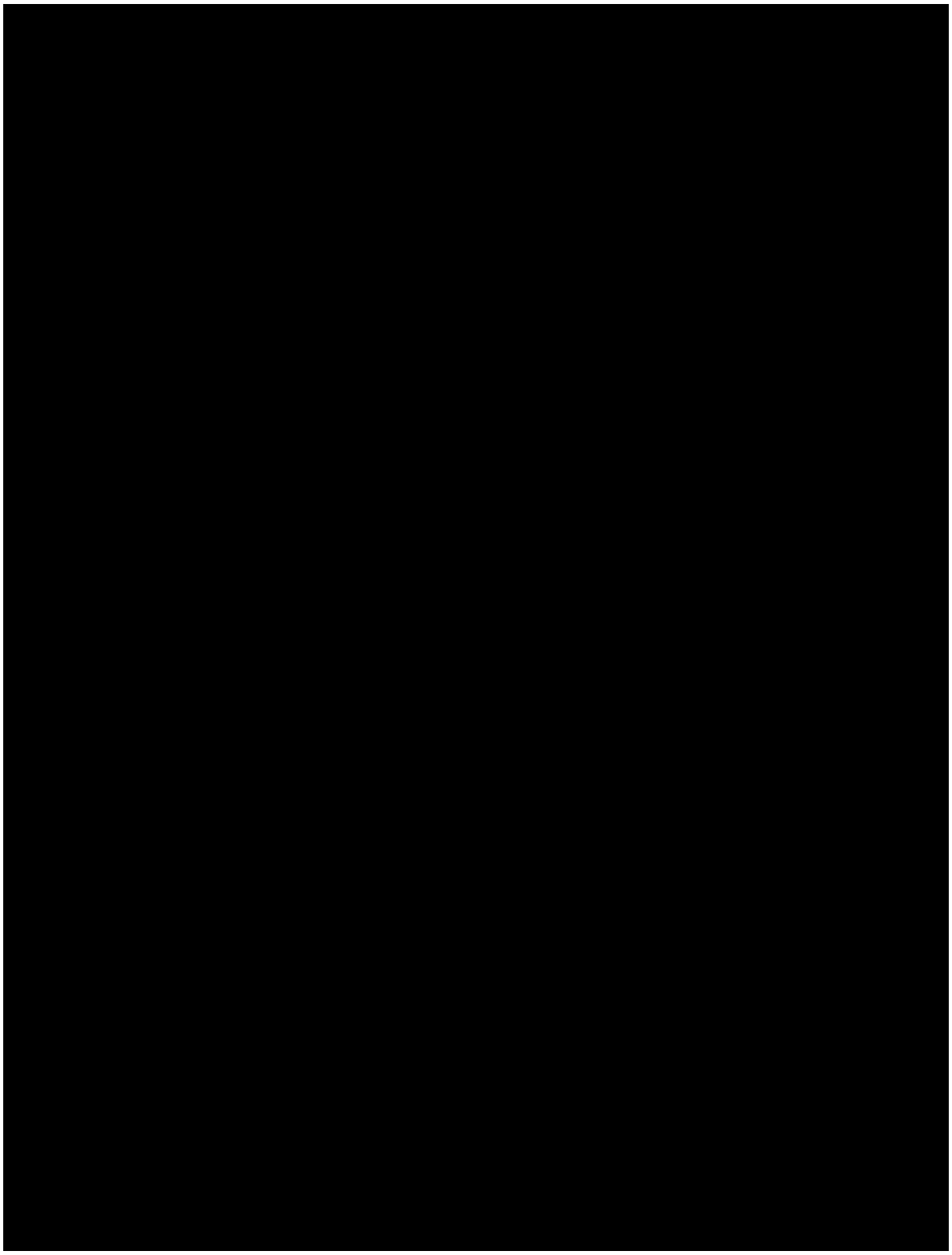
[redacted]

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**



Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**



Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

3.5 Formulation

ADVM-022 drug product is formulated in a buffer composed of 180 mM NaCl, 5 mM Na_2HPO_4, 5 mM NaH_2PO_4, and 0.001% Poloxamer 188 at pH 7.3. The ADVM-022 drug product is supplied as a sterile-filtered, frozen suspension in a sterile, ready-to-use 0.5 mL Crystal Zenith® vial which contains approximately 0.25 mL of investigational medicinal product. The vial is stoppered with a sterile, ready-to-use stopper made of chlorobutyl and sealed with a sterile aluminum seal. The filled vials are placed in an outer carton and stored at ≤ -60°C.

3.6 Dose Justification

[redacted] Other anti-VEGF treatments such as aflibercept have been studied using the same doses from their nAMD studies in their DME studies. These studies subsequently demonstrated that those treatments were also safe and efficacious in DME.

[redacted]

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

[redacted]

4.0 CLINICAL STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

- To assess the durability of a single IVT injection of ADVM-022

4.1.2 Secondary Objectives

Secondary Objectives:

- To assess the safety and tolerability of ADVM-022
- To evaluate the effect of ADVM-022 on macular edema
- To evaluate the effect of ADVM-022 on Best Corrected Visual Acuity (BCVA)
- To evaluate the effect of ADVM-022 on Diabetic Retinopathy Severity Scale (DRSS) score
- To assess the need for rescue aflibercept (2 mg IVT)
- To assess the effect of a preceding dose of aflibercept (2 mg IVT) prior to ADVM-022 administration

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

- To evaluate the effect of ADVM-022 on development of vision threatening complications (including anterior segment neovascularization, vitreous hemorrhage, or tractional retinal detachment)

4.2 Endpoints

4.2.1 Primary Endpoints

Time to worsening of DME disease activity in the study eye, as defined by the occurrence of either:

- An increase in CST > 50 μm as assessed by SD-OCT compared to the lower of the two CST measurements recorded at Day 1 or Week 4
- A loss of > 5 letters in BCVA due to worsening DME disease activity compared to the higher of the two BCVA measurements recorded at Day 1 or Week 4

4.2.2 Secondary Endpoints

Unless specified otherwise, the secondary endpoints are based on outcome measures for the study eye.

- Incidence and severity of ocular and non-ocular adverse events (AEs)
- Change from Baseline in central subfield thickness (CST) and macular volume over time through Week 96
- Change from Baseline in BCVA over time through Week 96
- Frequency of rescue aflibercept (2 mg IVT) in the study eye over time during the study
- Incidence of 2-step and 3-step improvement in DRSS score over time through Week 96
- Incidence of 2-step and 3-step worsening in DRSS score over time through Week 96
- Occurrence of vision threatening complication (anterior segment neovascularization, vitreous hemorrhage, or any other high-risk proliferative DR, or tractional retinal detachment) over time through Week 96
- Incidence of CST <300 μm over time through Week 96
- Incidence of clinically significant findings via physical examinations, ocular examinations, imaging, and laboratory evaluation

5.0 CLINICAL INVESTIGATION PLAN

5.1 Study Design

This is a multi-center, randomized, double-masked, controlled, parallel-group study to evaluate the efficacy, safety and tolerability of a single IVT injection of ADVM-022. Two doses of ADVM-022 will be investigated.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Subjects with initial diagnosis of DME within 6 months of screening and have received up to 2 prior injections of anti-VEGF therapy are eligible for enrollment.

Approximately 33 eligible subjects will be randomized to one of 5 arms. Arm 1 (n=6) will receive ADVM-022 6×10^{11} vg/eye with a preceding aflibercept dose. Arm 2 (n=6) will receive ADVM-022 6×10^{11} vg/eye of without a preceding aflibercept dose. Arm 3 (n=6) will receive ADVM-022 2×10^{11} vg/eye with a preceding aflibercept dose. Arm 4 (n=6) will receive ADVM-022 2×10^{11} vg/eye of without a preceding aflibercept dose. Arm 5 (n=9) will receive aflibercept only (active control). To maintain masking of the treatment assignment, subjects assigned to the arms with no preceding aflibercept on Day 1 or to the arm with no ADVM-022 on Day 8 will receive a sham ocular injection on the corresponding visit. Only one eye per subject will be selected as the study eye. If both eyes are eligible, the eye with the worse BCVA will be the study eye.

Subjects will be randomized to the following treatment arms in Table 3.

Table 3: Study Arms

Arm	N	Day 1 IVT Aflibercept or Sham	Day 8 ADVM-022 Dose (vg/eye)
1	6	Aflibercept	6×10^{11}
2	6	Sham	6×10^{11}
3	6	Aflibercept	2×10^{11}
4	6	Sham	2×10^{11}
5	9	Aflibercept	Sham

After the assigned IVT injections on Day 1 and Day 8, all subjects will return to the clinic on Week 2, Week 4, and then every 4 weeks up to Week 96. To maintain masking, both subjects and the site personnel who conduct outcome assessments were originally masked to the treatment assignment throughout the study. Emergency unmasking for all subjects has been required, as determined by the Sponsor with input from the Data Monitoring Committee, to preserve subject safety. The study has in effect become an open-label study, in which all prior masked roles will be able to continue study participation in an unmasked manner.

5.1.1 [redacted]:

[redacted]

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

5.1.2 Rescue Treatment:

Starting at Week 8, subjects will receive rescue aflibercept (2 mg IVT) if they meet any of the following:

- Increase in CST > 50 μm as assessed by SD-OCT compared to the lower of the two CST measurements recorded at Day 1 or Week 4
- Loss of > 5 letters in BCVA due to worsening DME disease activity compared to the higher of the two BCVA measurements recorded at Day 1 or Week 4

After initial rescue treatment administration, [redacted] Primary Investigator.

Only intravitreal aflibercept injection (Eylea) is to be used for any rescue treatment unless prior approval by medical monitor.

Aflibercept should not be injected in eyes with active inflammation. A minimum of 21 days is required between rescue aflibercept injections.

5.1.3 Data Monitoring Committee (DMC):

An independent DMC will monitor safety and study conduct on an ongoing basis. Members of the DMC will be independent from the Sponsor and will follow a charter that outlines the DMC's roles and responsibilities. The DMC will meet every 3-6 months (frequency adjustable as required) to evaluate unmasked ocular and non-ocular safety events, with emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, and clinically significant decreases in BCVA. The DMC will also meet on an ad hoc basis if stopping rules are met as outlined below. The DMC may recommend stopping the study early for safety reasons. After reviewing the data, the DMC will provide a recommendation to the Sponsor as described in the DMC Charter. Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs).

5.1.4 Stopping Rules:

Enrollment will be suspended if any of the following sight threatening events occur:

- A decrease of ≥ 30 letters in BCVA in the study eye compared with the prior visit
- A surgical intervention (i.e., conventional surgery, vitrectomy) to prevent permanent loss of sight.
- Severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitreous cells)

In addition, enrollment will be suspended if any serious adverse event potentially related to ADVM-022 occurs.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Any event that meets any of the above safety stopping criteria will be reported immediately to the Sponsor and enrollment and dosing will be suspended until the DMC has reviewed the data and made a recommendation to the Sponsor.

The regulatory authorities and the Investigators, and each site's IRB and other appropriate institutional regulatory bodies will be promptly notified 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

5.2 Study Duration

Duration of subject's participation in the study will be approximately 100 weeks for each subject (including up to 4-week screening period).

5.3 Study Population

Subjects with newly diagnosed DME (diagnosis within 6 months of screening) that have received up to 2 prior injections of anti-VEGF therapy in the study eye.

5.4 Allocation to Treatment

Each subject will be assigned a unique subject number after signing the informed consent. Subjects who complete the study screening assessments and meet all the eligibility criteria will be scheduled to enroll into the study and randomly assigned to one of the 5 treatment arms on Day 1. The planned allocation targets to have 6 subjects each for the four ADVM-022 arms.

5.5 Masking and Minimization of Bias

This is a double-masked study. Subjects and the designated masked study personnel will be masked to subject's treatment assignment throughout the study. There must be a minimum of two physicians per site to fulfill the masking requirements of the study. A masked and unmasked investigator are required to be present for the Day 1 and Day 8 visits, thereafter only the masked investigator is required to be present.

The roles and responsibilities for masked and unmasked personnel at the investigational site will be clearly documented on the Delegation of Authority Log. Once assigned and executed, these roles should not be switched during the conduct of the study. In unforeseen circumstances, a site can notify the Sponsor or designee for a switch of the study staff member from the masked role to the unmasked role but not vice versa.

As unmasking of all subjects has occurred prior to the end of the study, the study in effect has become an open-label study, in which all prior masked roles will be able to continue study participation in an unmasked manner.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

5.5.1 Masked Roles

If qualified, the study site personnel with masked role can take on any other masked role tasks except for tasks performed by the BCVA examiner. The designated roles for masked study site personnel include:

- Assessor physician (typically the principal investigator) who evaluates all pre-treatment assessment as well as all safety and disease activity assessment at all visits
- Photographer(s) and OCT technician(s)
- Study Coordinator(s) who have any interaction with study subjects including assessments
- BCVA examiner who will be masked to both the assigned treatment and the location (OD, OS) of the study eye. The BCVA examiner will have no access to subjects' medical record or the BCVA score from subjects' previous visits and may have access only to a subject's refraction data from previous visits. The BCVA examiner is not allowed to perform any other task involving direct subject care.

Additionally, study CRO staff (except those who are responsible for drug accountability or randomization), sponsor clinical study team, the Central Reading Center and the Central Lab personnel will be masked.

5.5.2 Unmasked Roles

Every effort should be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. There should be no more than six unmasked personnel at a study site at one time. In certain circumstances, the total number of unmasked personnel might be increased after discussion with and approval by the Sponsor. Any other study personnel not listed below will be in the masked roles.

- Treatment administrator: a retina specialist or a qualified ophthalmologist who is designated to perform the study treatment administration at Day 1 and Day 8. He/she can conduct assessment prior to randomization visit as well as the post-treatment procedure (i.e., IOP, indirect ophthalmic examination and slit lamp) including the optional aqueous humor sample collection. The person in this role will treat any adverse events that occur during or shortly after the study treatment administration; however, will not evaluate the causality of adverse events which is the responsibility of the masked assessor physician.
- Either the assessor physician or the treatment administrator can administer rescue aflibercept (2 mg IVT).
- Coordinator(s) and Pharmacist: A designated personnel who receives IMP and prepares the study treatment at Day 1 and Day 8. The person in this role, if qualified, can be assigned to measure post-dose IOP. If the site uses a pharmacy, then the unmasked role is also assigned to the pharmacist who performs study treatment related tasks per the Delegation of Authority Log.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

5.6 Emergency Unmasking

If unmasking a particular subject is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment) the investigator should contact the medical monitor directly.

Emergency unmasking for all subjects has been required, as determined by the Sponsor with input from the Data Monitoring Committee, to preserve subject safety. The study has in effect become an open-label study, in which all prior masked roles will be able to continue study participation in an unmasked manner. The unmasking process and sharing of subject treatment assignments will be communicated by the Sponsor or designee and must be documented properly at the site and sponsor levels.

5.7 Dispensing Instructions

Each subject that has met the eligibility criteria will be assigned a treatment arm based on a randomization procedure. The unmasked site staff is responsible for dispensing the proper treatment per the assigned treatment arm. [redacted].

5.8 Investigational Medicinal Product Accountability and Reconciliation

The unmasked designee will perform ADVM-022 accountability at the investigational site which requires reconciliation between the amount of ADVM-022 shipped to the investigational site, treatment assignment and dispensation.

5.9 Method of Administration

Both ADVM-022 and aflibercept will be administered via IVT injection, as per the IMP Manual. IVT injection should not be administered if active inflammation is present. Aseptic technique with povidone-iodine should be used with topical or subconjunctival anesthesia. Other than specified in the protocol, post-injection care and medication regimen will be performed as per institutional standard of care.

5.10 [redacted]

[redacted]

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

6.0 SUBJECT SELECTION CRITERIA AND WITHDRAWAL

6.1 Selection Criteria

Subjects must meet the following criteria to be included in this study. The subject must have an initial diagnosis of DME within 6 months of screening and have received a maximum of 2 prior anti-VEGF injections to be potentially eligible for this study.

6.2 Screening Records

All screened subjects will be assigned a unique number. A screening log or system will record the following minimum information:

- Subjects screening number
- Randomization Status
- Screen Fail reason (if applicable)

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

6.3 Inclusion Criteria

1) Male or female subjects, age ≥ 18 years of age
2) Type 1 or 2 diabetes mellitus
3) Ability and willingness to provide informed consent to participate in the study requirements and visits prior to any study procedure
4) Vision at Screening visit:
   a) Study Eye-BCVA 78 to 50 ETDRS letters, inclusive (approximate Snellen equivalent 20/32 to 20/100)
   b) Non-study eye-BCVA 35 ETDRS letters or more (approximate Snellen equivalent of 20/200 or better)
5) CST of study eye at Screening visit of ≥ 325µm using Heidelberg Spectralis® with center-involving IRF (center 1 mm)
6) A decrease in vision in the study eye determined by the investigator to be primarily due to DME
7) Initial DME diagnosis within 6 months from screening
8) Up to 2 prior injections (0, 1, or 2) of anti-VEGF in the study eye
   a) If a prior anti-VEGF has been administered to the study eye, in the judgement of the Investigator, there must have been a meaningful CST response (e.g. ≥ 10% reduction) and no adverse reaction to anti-VEGF (e.g. inflammation)
9) A minimum 60-day interval is required between the last anti-VEGF injection in the study eye and randomization on Day 1

6.4 Exclusion Criteria

Participants with any of the following conditions are ineligible:

6.4.1 General Exclusion Criteria

[redacted]

2) Any condition that, in the opinion of the investigator, could contraindicate the use of the investigational drug, ADVM-022, or that might affect interpretation of the study results or that renders the patient at high risk for treatment complications
3) Received an investigational medicinal product within 60 days or 5 half-lives prior to dosing with ADVM-022, whichever is longer
4) Prior ocular gene therapy
5) History of allergy to aflibercept, corticosteroid, or fluorescein dye or sodium fluorescein used in angiography (mild allergy amenable to treatment is allowable)

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

6) Pregnancy
   a) Women who ever intend to become pregnant
   b) Women who are currently or ever intend to breastfeed
   c) For women of childbearing potential (a woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (>12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of both ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements):
      i) May participate only if they have a negative pregnancy test at screening
      ii) Must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate <1% per year:
         (1) Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices
         (2) Contraception methods that do not result in a failure rate of < 1% per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
7) History or evidence of any of the following cardiovascular disease within 6 months of dosing:
   a) Severe cardiac disease (e.g., New York Heart Association [NYHA] Functional Class III or IV) or clinical evidence of unstable angina
   b) Acute coronary syndrome, myocardial infarction or coronary artery revascularization
   c) Ventricular tachyarrhythmias requiring ongoing treatment, or uncontrolled arrhythmia
   d) Uncontrolled hypertension defined as systolic blood pressure (SBP) >160 mmHg or a diastolic blood pressure (DBP) >100 mmHg, despite using BP–lowering medication within the screening period. If BP-lowering medications are required, subject should be on a stable dose of the same medication continuously for 30 days prior to randomization. History of cerebrovascular accident or transient ischemic attack
8) Any history of ongoing bleeding disorders. The use of aspirin or other anticoagulants (e.g., Factor Xa inhibitors) is not an exclusion.

Adverum Biotechnologies, Inc.
Clinical Protocol No. ADVM-022-04
ADVM-022 (AAV.7m8-aflibercept)
Amendment 7.0, 05 August 2021

9) HbA1C >10%; or history of diabetic ketoacidosis within 3 months prior to randomization; or subjects who, within the last 3 months, initiated intensive insulin treatment (a pump or multiple daily injection) or plan to do so in the next 3 months.

[redacted]

12) History of malignancy within the last 5 years except for the following adequately treated:
    a) Local basal cell or squamous cell carcinoma of the skin
    b) Carcinoma in situ of the cervix or breast
    c) Papillary, noninvasive bladder cancer
    d) Prostate cancer Stage 1 and 2 for which observation is clinically indicated with stable prostate-specific antigen (PSA) for 6 months
    e) Any other cancer that has been in complete remission for at least 2 years or considered surgically cured
13) Known to be positive for HIV or active viral hepatitis (unless documented cure after treatment for Hepatitis C)
14) Known history of syphilis
15) Known severe renal impairment, as indicated by estimated CrCl <30 mL/min (by Cockcroft-Gault calculation); need or anticipated need for hemodialysis during the study period
16) Other significant laboratory abnormalities that the Investigator feels may compromise the subject's safety
17) Any febrile illness within 1 week prior to randomization

6.4.2 Ocular Exclusion Criteria (Study Eye)

18) High-risk PDR at time of screening, defined as: any vitreous or preretinal hemorrhage, neovascularization elsewhere >1/2-disc area within an area equivalent to standard ETDRS 7-field on clinical examination, or neovascularization of disc > 1/3-disc area on clinical examination
19) Any prior focal or grid laser photocoagulation or any prior PRP in the study eye

[redacted]

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

[redacted]

23) History of retinal disease in the study eye other than diabetic retinopathy including age-related macular degeneration (in either eye), retinal vein occlusion, retinal arterial occlusion, pathologic myopia, etc.

24) Any current or history of ocular disease other than DME that, could reduce the potential for visual improvement, confound assessment of the macula or require medical or surgical intervention during the study (e.g. significant cataract, macular traction) or any evidence of posterior subcapsular cataract

25) History of cataract extraction or YAG capsulotomy within 3 months before Day 1

26) History of retinal detachment (with or without repair) in the study eye

27) History of trabeculectomy or glaucoma shunt or minimally invasive glaucoma surgery (MIGS)

[redacted]

6.4.3 Ocular Exclusion Criteria (Fellow or Study Eye)

[redacted]

36) Known history of ocular HSV, VZV, or CMV including viral uveitis, retinitis or keratitis

37) Evidence of external ocular infection, including conjunctivitis, chalazion or significant blepharitis

38) History of ocular toxoplasmosis

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

6.5 Subject Withdrawal

Subjects have the right to withdraw their informed consent to participate in the study at any time. However, every effort should be made to retain subjects in the study to monitor their safety. If a subject chooses to discontinue, the subject is encouraged to return to clinic to be followed up on subject's disease status and complete study assessment as specified by protocol. Any missing assessment will be recorded as the protocol deviation.

A subject may discontinue the study for the following reasons:

- Withdrawal of consent by the subject
- Lost to follow-up
- Investigator's decision (such as chronic noncompliance, adverse event(s) that put the safety of the subject at risk, significant protocol deviation, or best interest of the subject)
- Study termination by the Sponsor
- Death

Subjects who withdraw prior to receiving the study treatment (ADVM-022 IVT or Sham ocular injection) on Day 8 after randomization will not be replaced directly. However, the treatment allocation will be adjusted accordingly for subsequently enrolled subjects to achieve a target of 6 treated subjects/arm for the 4 ADVM-022-treated arms and 9 treated subjects in Arm 5.

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. At least two phone calls and a registered letter should be documented before considering subject lost to follow-up. When a subject withdraws before completing the study, attempts of follow-up information should be documented in the source documents to include reasons of withdrawal.

7.0 STUDY ASSESSMENTS AND PROCEDURES

The study assessments and procedures are outlined in the Schedule of Assessments, Section 18.1.

In the event of an event that limits the ability of a site to conduct in-person clinic visits (e.g., in the case of a pandemic), certain safety assessments including medical history and concomitant medication information can be collected via phone calls. The contact should be documented in the subject's source document and the CRF should be updated accordingly. Additional ocular examination and imaging assessments should be captured in the presence of active intraocular inflammation and/or significant vision loss (greater than or equal to 15 letters loss from Baseline), refer to the management of i[redacted] (Section 5.11) and schedule of assessments (Section 18.1 and Section 18.2). Additional assessment requirements may be reduced based on severity and location of the inflammation on any subsequent follow-up visits.

The procedure descriptions are as follows:

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

7.1 Informed Consent

Informed consent confirming a subject's willingness to participate in the study must be obtained before performing any study-specific screening tests, evaluations, or procedures. Subjects will be provided with an IRB-approved informed consent form (ICF) detailing the IMP, study assessments, and study procedures. Prior to being asked to sign the ICF, subjects will be given time to review the study information and ask questions. Acceptable remote methods of consent include mailing, emailing, and faxing of consent documents and telephone or video contact.

7.2 Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets the inclusion/exclusion criteria prior to randomization on Day 1 (Section 6.3 and Section 6.4). In addition to the Investigator, the Central Reading Center will review imaging as part of eligibility assessment.

7.3 Medical History, Ophthalmic History, and Demographics

The subject's relevant medical and ophthalmic history will be collected and recorded. The medical history collection period is defined as disease history up until screening. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis, prior treatments, dates administered, and responses will be recorded.

7.4 General Physical Examination and Vital Signs

The general physical examination (PE) will be conducted at screening and End of Study (EOS)/or Early Termination visit. It consists of body system examination for general appearance, neurologic, HEENT (head, eyes, ears, nose, and throat), neck, cardiovascular, respiratory, abdomen, extremities, skin, and weight. Height will be measured at screening only. At the EOS/or Early Termination visit, the physical examination will assess if any changes in the subject's physical condition have occurred since the Screening examination. A targeted physical examination should be conducted as needed for the evaluation of AEs.

Vital signs will consist of blood pressure, pulse rate, body temperature, and respiratory rate. Systolic and diastolic blood pressure and pulse rate will be measured after subjects have been at rest (seated) for at least 5 minutes.

7.5 ECG Evaluation

A 12-lead Electrocardiogram (ECG) will be taken for each subject at Screening and EOS/or Early Termination Visit. The Investigator will assess whether the ECG is normal, abnormal and not clinically significant, or abnormal AND clinically significant.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

7.6 Laboratory Tests

Clinical Laboratory, Vector Expression and Immune Response tests will be performed centrally as specified in the Schedule of Assessments. The procedures for sample collection, process and shipment are described in the Study Laboratory Manual.

7.6.1 Clinical Laboratory Tests

The following Clinical Laboratory Tests will be conducted for the study:

- Chemistry
- CBC
- HbA1C
- Urinalysis
- Serum or urine Pregnancy Testing (females of child-bearing potential)
- HLA-B27 genotyping

A detailed listing of clinical laboratory tests is outlined within the Study Laboratory Manual. Laboratory reports will be made available to the Investigator in a timely manner to ensure appropriate clinical review.

7.6.2 [redacted]

[redacted]

7.7 Full Ophthalmic Examination

The assessment will include an ophthalmologic exam, Intraocular Pressure (IOP), and indirect ophthalmoscopy.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

The ophthalmic examination will consist of an external examination of the eye and adnexa, routine screening for eyelid/pupil responsiveness (including but not limited to blepharoptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light, and afferent pupillary defect), and slit-lamp examination (eyelids, conjunctiva, cornea, lens, iris, anterior chamber). The slit-lamp examination will examine the anterior ocular structures and will be used for grading any findings. If any finding is noted during the slit-lamp examination, at any visit, the severity will be graded by the Investigator and the finding should be described as clinically significant or not clinically significant.

The IOP measurements will be performed using a Goldmann applanation tonometer or Tono-pen™, as specified in the Schedule of Assessments. The same method of IOP measurement must be used throughout the study for each individual subject. IOP measurements will be performed prior to any IVT injection and prior to dilating eyes, using the same method throughout the study. Every effort should be made to have IOP measurements performed at approximately the same time of day and using the same type of instrument for a given subject throughout the study, whenever possible. Day 1 and Day 8 visits will require pre-injection and post-injection (30 minutes after injection) IOP measurements. Study eye post injection IOP measurement is also required following any rescue aflibercept injection. Any post injection IOP measurements of the fellow eye are optional.

The dilated indirect ophthalmoscopy examination will include an evaluation of posterior segment abnormalities of the vitreous, optic nerve, peripheral retina, and retinal vasculature. If any finding is noted during the ophthalmoscopy, at any visit, the severity will be graded by the Investigator and the finding should be described as clinically significant or not clinically significant. Day 1 and Day 8 visits will require pre-injection and post-injection indirect ophthalmoscopy assessments. Post injection indirect ophthalmic exam of the study eye is also required following any rescue aflibercept injection. Post injection indirect ophthalmic examinations of the fellow eye are optional.

7.8 Refraction and Visual Acuity

Refraction and BCVA will be measured by a trained and certified visual acuity examiner(s) at the study sites.

Visual acuity measurements will be measured at a starting distance of 4 meters, prior to dilating eyes. A visual acuity specifications document, procedure manual, and training materials will be provided to the investigational sites, and examiner certification will be obtained. The visual acuity examination room must be certified prior to any visual acuity examinations. The full refraction and VA procedure will be provided in the [redacted].

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

7.9 Imaging

All imaging procedures will be described in a [redacted]. All images should be taken according to the Schedule of Assessments. All images should be kept at the site with copies sent to the Central Reading Center.

7.9.1 Spectral Domain Optical Coherence Tomography - SD-OCT (Retinal and Optional Anterior Segment Imaging)

SD-OCT is an interferometric technique that provides depth-resolved tissue structure information encoded in the magnitude and delay of the back-scattered light by spectral analysis of the interference fringe pattern. The same machine should be used for all study visits. Anterior segment images are optional if a site does not have the capability to take images of the anterior segment.

If a subject received anti-VEGF injections at visits prior to study randomization, OCTs from those visits should be collected and delivered to the central reading center.

7.9.2 Optional Optical Coherence Tomography Angiography (OCT-A)

OCT-A is an imaging technology that provides volumetric, three-dimensional maps of the retina and choroid as well as information on blood flow. This procedure is optional and will only be utilized at sites with OCT-A instruments. There are two types of OCT-A, swept-source and spectral-domain. Swept-source imaging should be used where available. If a swept-source instrument is not available and a spectral-domain instrument is available, then the spectral domain instrument should be used.

7.9.3 Ultra-wide Field Fundus Photography and Iris Photography

A standardized procedure for the collection of ultra-wide field fundus digital photographic images of the retina, optic disc, and macula will be followed. In addition, photographs of the iris will be taken prior to dilation.

7.9.4 Ultra-wide Field Fluorescein Angiography

A standardized procedure for examining the retinal circulation and vessel permeability using a dye-tracing method will be followed. This involves injection of sodium fluorescein into the systemic circulation, after which an angiogram is obtained by digitally photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490 nm.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

7.9.5 Optional Ultrasound Biomicroscopy (UBM)

Ultrasound Biomicroscopy (UBM) is a technique primarily used for imaging the anatomy and associated pathologies of the anterior segment (AS) of the eye. UBM uses a higher frequency transducer (35-100 MHz) than conventional ultrasound. UBM has utility in diagnosis and management of uveitis. UBM is optional at sites that have access to the appropriate equipment. Both eyes should be imaged, according to the Schedule of Assessments.

7.10 Laboratory, Biomarker and Other Biological Specimens

All laboratory specimens should be collected as indicated in the Schedule of Assessments. Sample collection and handling guidelines will be described in the laboratory manual.

7.10.1 Optional Aqueous Humor Sampling

If the subject consents, the aqueous humor sample should be collected by a qualified study staff, using aseptic procedure according to local guidelines. As indicated in the schedule of assessments, aqueous humor samples should also be obtained on visits in which a rescue aflibercept injection is administered. Aqueous humor samples should be collected prior to injection of aflibercept. Collection of aqueous humor samples is not required from subjects randomized to Arm 5 (sham treatment) following the unmasking of the study.

Aqueous humor samples may be analyzed for levels of aflibercept, [redacted]. Remaining samples will be analyzed for additional biomarkers.

7.10.2 Optional Vitreous Humor and Other Ocular Tissue Sampling

If vitrectomy is medically necessary and the subject consents, an optional vitreous humor sample can be obtained. Vitreous humor samples will be analyzed primarily for aflibercept concentrations. If any other surgical procedures become medically necessary in the study and/or fellow eye during the course of the study, other ocular tissues may be provided, including aqueous or vitreous humor and lens to be analyzed for other biomarkers. The remaining samples may be analyzed for other biomarkers.

8.0 REQUIRED, CONCOMITANT AND EXCLUDED MEDICATIONS

8.1 Required Medications

8.1.1 [redacted]

[redacted]

8.1.2 Eylea® (aflibercept)

Eylea (aflibercept) is indicated for the treatment of patients with DME; it is commercially available (Eylea USPI).

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

8.2 Concomitant Treatments

Concomitant treatments are any prescription or over-the-counter drugs and medical procedure other than protocol specified procedural medications and pre- and post- IVT injection medications used by a subject 30 days before Day 1 until the subject's end of study or early termination visit.

At the discretion of the evaluating physician, subjects may continue to receive all medications and standard treatments administered for other conditions except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Prohibited Medications and Treatments

The following medications are prohibited during the study:

- Any systemic anti-VEGF agent including bevacizumab
- Systemic drugs known to cause macular edema (e.g., fingolimod, tamoxifen, chloroquine/hydroxychloroquine)
- Any anti-VEGF agent in the study eye other than the study drug or aflibercept IVT 2 mg, as defined in this protocol
- [redacted]
- Systemic Immunosuppressive drugs (e.g., intravenous steroids, methotrexate, azathioprine, cyclosporin, adalimumab, infliximab, etanercept). Inhaled or topical steroids and NSAIDs are allowed
- Use of any other investigational study treatment or device

  Note: Subjects who develop high-risk PDR in the study eye may receive panretinal photocoagulation (PRP) after receiving rescue aflibercept.

  Note: Subjects with visually significant cataract cannot be enrolled in the study but if a cataract develops during the study, cataract surgery in the study eye may be performed if clinically indicated and is scheduled $\geq$ 90 days after ADVM-022 administration and/or $\geq$ 7 days after the last injection of aflibercept.

  Note: Subjects who develop DME in the fellow (non-study) eye may receive standard of care therapy.

9.0 ADVERSE EVENT HANDLING AND SAFETY REPORTING

9.1 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-022. For AEs and SAEs, the reporting period begins at the time the 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 on Day 1, only AEs (non-serious and serious) assessed as related to study procedures should be reported. Events that occurred after the informed consent but prior to Day 1 treatment administration that are not related to study procedures should be recorded as Medical History Events. After treatment administration, all clinically significant AEs 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) for any ongoing IMP related AEs and/or SAEs until they are considered resolved or 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/AE be followed longer.

However, any clinically significant safety assessment that is associated with DME shall not be reported as an AE or SAE, unless judged by the Investigator to be more severe than expected for the subject's condition. Progression of the disease under study will be captured as an efficacy outcome.

9.2 Adverse Events

An AE is any untoward medical occurrence in an enrolled subject regardless of its causal relationship to the IMP including but not limited to:

- Any new disease or exacerbation of an existing condition
- Constellations of individual signs, symptoms and laboratory values should be reported as the underlying diagnosis when possible (e.g., elevated WBC, cough and fever associated with pneumonia should not be reported as individual AEs but rather as the unifying condition of pneumonia)
- Recurrence of a sporadic medical condition (e.g., fever) not present at Baseline
- Adverse events related to a protocol-mandated intervention, including those that occur prior to study treatment (e.g., aflibercept injection)

9.3 Definition of Serious Adverse Event

An SAE is any untoward medical occurrence in an enrolled subject, regardless of its causal relationship to the ADVM-022, that results in:

- death

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

- a life-threatening condition
- inpatient hospitalization or prolongation of existing hospitalization
- 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.

9.4 Adverse Events of Special Interest (Immediately reportable to Sponsor)

Adverse events of special interest for this study are as follows:

- Sight-threatening adverse events: An adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - It causes a decrease of ≥ 30 letters in BCVA compared with the prior visit
  - It requires surgical or medical intervention (i.e., conventional surgery, vitrectomy) to prevent permanent loss of sight
  - It causes severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitreous cells)

All of the above-listed sight-threatening adverse events should be reported as serious adverse events, listing the underlying cause (if known) of the event as the primary event term.

9.5 Pregnancy-Related Event

Pregnancy is not regarded as an AE unless there is a suspicion that an ADVM-022 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 CRO 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 CRO.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

9.6 Eliciting 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).

9.7 Reporting and Documenting Adverse Events

AEs identified from any study data (e.g., laboratory values, PE findings, ophthalmic examination) for from review of other documents relevant to subject safety during the study are to be documented on the AE eCRF. Information to be collected includes event term, time of onset; Investigator assessment of seriousness, severity, and relationship to ADVM-022; 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 comorbidities 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 or AE of Special Interest must be reported to the Sponsor or its designee immediately e.g., within 24 hours after the time site personnel first learn about the event. An event of interest reported will warrant further investigation by the Sponsor prior to dosing additional subjects. The following contact information is to be used for SAE reporting:

CRO: Contact Information for Submission of SAE Report Form

[redacted]

Phone:

[redacted]

Fax:

[redacted]

Email: [redacted]

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

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Adverum/CRO has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of ADVM-022. Adverum/CRO will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.

Investigator safety reports are prepared for suspected unexpected SAEs according to local regulatory requirements and Adverum/CRO policy and are forwarded to Investigators, as necessary.

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

9.8 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 on the following scale:

Mild: The AE is noticeable but does not significantly impair the subject's daily activities.

Moderate: the AE reduces or impairs normal daily activity but is not incapacitating.

Severe: the AE is incapacitating and results in an inability to perform normal daily activity.

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.

9.9 Assessment of Causality

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

Investigator should assess potential causes of each adverse event and events should be considered related if there is "a reasonable possibility of a causal relationship" rather than if "a causal relationship cannot be ruled out." When assessing causality, Investigators should assess biological balancing — the probability that the suspect drug caused the Adverse Event (AE) must be weighed against the probability that an alternative candidate caused it. The relationship or association of study treatment in causing or contributing to the AE is to be characterized using the following classification and criteria:

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Definitely Related:	A definite causal relationship exists between the study treatment and the AE; including a plausible time relationship to study treatment, and it cannot be explained by underlying or concurrent disease or other drugs/ exposures.
Likely Related:	There is a reasonable possibility that study treatment caused the adverse event; the event is unlikely attributed to underlying or concurrent disease or other drugs/exposures (i.e., alternative explanation). There is a reasonable time sequence to administration of the study drug.
Unlikely Related:	Underlying or concurrent disease or other drugs/exposures provide plausible alternative explanations. Temporal relationship to study treatment administration makes a causal relationship improbable.
Not Related:	There is no association between the study treatment and the reported event; there is a clear alternative explanation; a causal relationship is non-plausible.

9.10 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 of a subject death while participating in the study, the Investigator should request a full autopsy report, if available.

9.11 Overdose and Reporting

An overdose is any dose of study treatment given that exceeds the dose described in the protocol. 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. There is no specific antidote for overdose of study treatment. 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.

10.0 ASSESSMENT OF EFFICACY

The efficacy of ADVM-022 in the treatment of DME will be assessed by the following measures. Baseline values for BCVA and SD-OCT endpoints refer to pre-treatment measurements taken on the Day 1 visit when aflibercept IVT or Sham ocular injection was administered.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

- BCVA – Vision will be assessed primarily through the BCVA expressed as an ETDRS score (number of letters correctly read). Maintenance of vision is classified if the subject has lost fewer than 15 letters in the ETDRS score compared to Baseline. Calculated endpoints will include the mean change from Baseline, the percent gaining at least 15 letters compared to Baseline, and the percent losing 15 or more letters compared to Baseline.
- Central subfield thickness – SD-OCT will be performed using approved equipment and standard techniques to evaluate thickness and fluid compared to Baseline values. Endpoints will include CST and macular volume and be assessed by the Central Reading Center.
- Aflibercept re-treatments – The incidence and timing of aflibercept injections given post ADVM-022 treatment over time.
- For each timepoint, DRSS will be determined by the Central Reading Center using ultra-wide field color fundus photography and compared to Day 1.
- Vision threatening complications (anterior segment neovascularization, diabetic macular edema, high-risk PDR development, vitreous hemorrhage, or tractional retinal detachment) as determined by ultra-wide field imaging and clinical examination by the Investigator.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

The durability of ADVM-022 will primarily be assessed through evaluation of the need for rescue aflibercept (2 mg IVT) due to worsening of DME disease activity. Disease activity and rescue aflibercept (2 mg IVT) received will be summarized descriptively. However, with 12 subjects at a given dose level of ADVM-022 versus 9 subjects receiving aflibercept only (Control), there is a 93.1% power for a 1-sided Fisher Exact Test at an alpha level of 0.05 to claim a significant reduction in the rate (in terms of proportion of subjects) of disease worsening (or of receiving any rescue aflibercept 2 mg IVT) during a given follow-up time (say, 24, or 48 weeks) when the true rate is 90% for the Control and 20% for the ADVM-022 treated. Table 5 summarizes the powers for the same hypothesis tests under several different assumptions in the rate of receiving any aflibercept injection.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Table 5: Power for 1-Sided Fisher Exact Tests at Various Rate Assumptions

Sample Size [a]	Rate: Control	Rate: ADVM-022 Treated	Power [b] (1-sided Fisher Exact, $\alpha = 0.05$)
N=12 ADVM-022 Treated versus N=9 Control	90%	17%	95.3%
		20%	93.1%
		25%	88.3%
	95%	17%	98.6%
		20%	97.7%
		25%	95.5%
N=6 ADVM-022 Treated versus N=9 Control	90%	17%	88.8%
		20%	85.6%
		25%	79.6%
	95%	17%	95.2%
		20%	93.2%
		25%	89.0%

[a] The sample sizes are not adjusted for dropouts.

[b] Power for the Fisher Exact test was based on binomial enumeration of all possible outcomes, which was performed using PASS 2019 v19.03.

This study was also designed to assess safety and tolerability of ADVM-022 in subjects with DME. If none of the subjects in a group have any untoward event, the 95% upper confidence limit of the event rate is 11.7% for a group size of 24 (the target number of subjects to receive ADVM-022), or 22.1% for a group size of 12 (the target number of subjects to receive each dose level of ADVM-022).

11.2 Analysis Populations

The main analysis population will include all randomized subjects who receive the study treatment on Day 8 (ADVM-022 IVT or Sham ocular injection). The summary will be based on the actual treatment received by the subject.

11.3 Statistical Methods

No formal statistical tests are planned for the study. All safety and efficacy variables will be summarized descriptively by treatment arm. Mean, standard deviation (SD), median and range will be provided for continuous variables; and frequency counts and percentages will be provided for categorical variables. Confidence intervals of the means and percentages will be provided at both 90% and 95% levels. Kaplan-Meier survival analysis will be utilized to derive median time to the first occurrence of DME disease worsening. All rescue aflibercept (2 mg IVT) received by each subject during the study will be summarized using statistical models for recurrent events. Mean cumulative function (MCF) curve over time will be plotted for the mean cumulative number of injections. Mixed-effect models for repeated measures (MMRM) will be

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

employed to explore the treatment effect on the change over time in BCVA and CST. The treatment effect on DRSS changes over time will be explored using generalized mixed models for categorical outcomes.

An interim analysis (IA) is planned after all subjects have been followed for 24 weeks. The detailed IA plan will be described in the Statistical Analysis Plan (SAP). As unmasking of all subjects has occurred prior to the end of the study, the study in effect has become an open-label study.

12.0 ETHICAL CONSIDERATIONS

12.1 Institutional Review Board / Institutional Biosafety Committee

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

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

12.2 Ethical Conduct of the Study

The study is to be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and Council of International Organizations of Medical Sciences (CIOMS) Ethical Guidelines, and in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Harmonised Tripartite Guideline E6: Good Clinical Practice; 21 Code of Federal Regulations (CFR); and applicable laws and regulations.

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

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

12.3 Subject Information and Consent

The study specific ICF and the informed consent process must comply with the Declaration of Helsinki, US Title 21 Code of Federal Regulations (CFR) Part 50, Health Insurance Portability and Accountability Act of 1996 (HIPAA) (if applicable), and local laws. The Investigator will draft the ICF, assent, and HIPAA authorization (if applicable) and submit the draft for review and comment by the Sponsor, and Investigator will submit the mutually agreed upon ICF, ascent, and HIPAA authorization (if applicable) to the IRB/IBC for approval.

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

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

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

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

13.0 INVESTIGATOR'S RESPONSIBILITIES

A complete list of Investigator responsibilities is outlined in the Clinical Trial Agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol, the Statement of Investigator, the general investigational plan, and applicable laws and regulations; will read and understand the Investigator's Brochure; will obtain IRB/IBC approval to conduct the study; will obtain informed consent from each study participant prior to their participation in the study; will maintain and supply to the Sponsor or designee, auditors, and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/IBC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/IBC according to the specifics outlined in

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

this protocol, which reports shall include an assessment of whether there is a reasonable possibility that the study drug caused the AE; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

14.0 SPONSOR RESPONSIBILITIES

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

14.1 Modification of the Protocol

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

14.2 Protocol Deviations

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

The Sponsor or designee will be notified of known significant protocol deviations by the Investigator. Protocol deviations found throughout the course of monitoring visits are to be documented by the clinical monitor. The IRB/IBC should be notified of all applicable protocol deviations, in accordance with reporting requirements of the IRB/IBC, in a timely manner by the Investigator.

14.3 Confidentiality

Investigators must comply with all applicable privacy laws and regulations (e.g., HIPAA). Information on maintaining subject confidentiality in accordance with individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process, either as part of the ICF or as a separate signed document. In the United States,

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

a site-specific HIPAA-compliant authorization form may be used. The Investigator or designee must explain to each subject that for the evaluation of study results and potential marketing approval, the subject's protected health information obtained during the study may be disclosed to the Sponsor and its designees, regulatory agencies, and the IRB/IBC.

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

14.4 Investigator's Report to the IRB/IBC

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

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

14.5 Records Retention

The Investigator is responsible for retaining documents as required by local law and applicable regulations, as well as ICH standards. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the ADVM-022. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

14.6 Financial Disclosure and Obligations

A separate financial agreement will be made between each Investigator and the Sponsor or its authorized representative. For this study, each principal Investigator and sub-Investigator (as designated on the Form FDA 1572) will provide a personally signed Financial Disclosure Form in accordance with 21 CFR Part 54. Each Investigator will notify the Sponsor or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

Neither the Sponsor nor its designee is financially responsible for further testing or treatment of any medical condition that may be detected in the subject at the time of the informed consent process. In the absence of specific arrangements, neither the Sponsor nor designee is financially responsible for further treatment of the subject's disease.

14.7 Liability and Insurance

In the event of a side effect or injury, appropriate medical care as determined by the treating physician/designee will be provided. The ICF will include a description of treatment in the event of a protocol-related injury and handling of the costs associated therewith, incorporating country-specific national regulations and / or local laws. Allocation of financial responsibility as between Sponsor and each individual participating site for the costs associated with such treatment will be as specified in the relevant CTA. Financial compensation for the lost wages, disability, or discomfort due the treatment with the ADVM-022 is not available. Insurance has been undertaken according to the laws of the countries where the treatment protocol will be conducted. An insurance certificate will be made available to the participating sites at the time of protocol initiation.

14.8 Publication Policy

The study data may be considered for reporting at a scientific meeting or for publication in a scientific journal. Authorship may be adjusted upon mutual agreements and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions. The data are the property of Adverum and cannot be published without the expressed written authorization of Adverum.

15.0 STUDY MANAGEMENT

15.1 Monitoring of the Study

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

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

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

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

15.2 Data Quality Assurance

The Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted, and that data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013) and all revisions thereof, and in accordance with the FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D—Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

15.3 Data Management

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

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

Authorized study site personnel (e.g., listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data. The CRFs exist within an electronic data capture (EDC) system with controlled access managed by the Sponsor or its authorized representative for this study.

Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system.

Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system.

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

Adverum Biotechnologies, Inc. **ADVM-022 (AAV.7m8-aflibercept)**
Clinical Protocol No. ADVM-022-04 **Amendment 7.0, 05 August 2021**

16.0 STUDY COMPLETION

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

The Sponsor has the right to terminate this study at any time at its discretion. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

17.0 REFERENCES

Dalkara D, Byrne LC, Klimczak RR, et al. In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous. *Sci Transl Med*. 2013;5(189):189ra76.

[redacted]

Eylea® Prescribing Information, Regeneron Pharmaceuticals, Inc. Tarrytown, NY.

Grishanin R, Vuillemenot B, Sharma P, et. al. Preclinical Evaluation of ADVM-022, a Novel Gene Therapy Approach to Treating Wet Age-Related Macular Degeneration. *Molecular Ther*. 2019 Jan 2;27(1):118-129.

Johnston SS, Wilson K, Huang A, et al. Retrospective Analysis of First-Line Anti-Vascular Endothelial Growth Factor Treatment Patterns in Wet Age-Related Macular Degeneration. Adv Ther. 2013;30:1111–1127. DOI 10.1007/s12325-013-0078-4.

Varma R, Bressler NM, Doan QV, et al. Prevalence of and Risk Factors for Diabetic Macular Edema in the United States. *JAMA Ophthalmol.* 2014;132(11):1334-1340.

Wang W and Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. *International Journal of Molecular Sciences*. 2018;19(1816).

Wubben, TJ and Johnson MW. Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions. *American J Ophthal*. 2019;204:13–18. https://doi.org/10.1016/j.ajo.2019.03.005