STATISTICAL ANALYSIS PLAN

for

Protocol: 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 2.0

DATE: 28-NOV-2022

STUDY INFORMATION

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SIGNATURE PAGE

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PROTOCOL NUMBER: ADVM-022-04, Version 7.0 05-August-2021

Primary Sponsor Representative: [redacted]

Signature: [redacted] 05/Dec/2022 08:03 PM EST Click or tap to enter a date.

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List of Abbreviations

6E11, 2E11	6 x 10^{11}, 2 x 10^{11} viral genomes/eye, respectively
AAV	Adeno-Associated Virus
AE	Adverse Event
AESI	Adverse Event of Special Interest
anti-VEGF	anti-Vascular Endothelial Growth Factor
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CBC	Complete blood count
CF	Count Fingers
CFP	Color fundus photography
CI	Confidence Interval
CRO	Clinical Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
CST	Central Subfield Thickness
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRSS	Diabetic Retinopathy Severity Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immune absorbent spot
EOS	End of Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein Angiography
HM	Hand Movement
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IVT	Intravitreal
LP	Light Perception
MEDDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
OD	Oculus Dexter (Right Eye)
OS	Oculus Sinister (Left Eye)
OU	Oculus Uterque (Both Eyes)
PDF	Portable Document Format
PT	Preferred Term
RAP	Retinal Angiomatous Proliferation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO DD	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for Adverum protocol ADVM-022-04, Amendment 7.0 dated 05 August 2021.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, titled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, titled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed at an interim analysis after all subjects have completed 24 weeks post-Day 1 (see [redacted] of the ADVM-022-04 protocol for Day 1 definition). The interim analysis is preplanned in the study protocol after subjects have been followed for 24 weeks (protocol Section 11.3), as is data analysis after subjects are followed for 48 weeks (also preplanned) and for 96 weeks. A 96 week data analysis has been incorporated in this SAP because of the Sponsor decision to unmask the study due to an unforeseen Suspected Unexpected Serious Adverse Reaction (SUSAR) in one subject. This SAP provides details of the subject characteristics, efficacy, and safety assessments that will be evaluated and the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol; any deviations in the analyses stated in the protocol are specified in SAP Section 18.0. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the clinical study report (CSR).

2. Study Objectives

2.1. Primary Objective

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

2.2. 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)

3. Study Endpoints

3.1. 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

3.2. Secondary Endpoints

Unless specified otherwise, the secondary endpoints are based on outcome measures for the study eye. Baseline values for BCVA and SD-OCT endpoints refer to pre-treatment measurements taken on Day 1 visit when aflibercept IVT or Sham ocular injection was administered. The secondary efficacy endpoints include the following:

- 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

3.3. Safety Endpoints

In addition to those stated as the secondary endpoints, safety will be assessed by findings/outcomes via the following procedures/assessments:

- General physical examination and vital signs
- ECG evaluation
- Clinical laboratory tests
- Pregnancy test, if applicable

- Full ophthalmic examination including external examination of eye and adnexa, slit-lamp biomicroscopy, intraocular pressure (IOP), and indirect ophthalmoscopy
- Spectral domain optical coherence tomography (SD-OCT)
- Anterior segment OCT
- OCT angiography (OCT-A)
- Ultra-wide field color fundus photography and Iris Photos
- Ultra-wide field Fluorescein angiography (FA)

3.4. Statistical Hypotheses

There are no pre-specified statistical hypotheses for this hypothesis generating study.

4. Study Design and Procedures

4.1. General 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.

34 eligible subjects will be randomized to one of the following 5 arms:

1. Arm 1 (n=6) will receive ADVM-022 6×10^{11} vg/eye with a preceding aflibercept dose.
2. Arm 2 (n=6) will receive ADVM-022 6×10^{11} vg/eye of without a preceding aflibercept dose.
3. Arm 3 (n=6) will receive ADVM-022 2×10^{11} vg/eye with a preceding aflibercept dose.
4. Arm 4 (n=7) will receive ADVM-022 2×10^{11} vg/eye of without a preceding aflibercept dose.
5. 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.

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.

All subjects will be on a prophylactic 10-week topical corticosteroid regimen of difluprednate starting on Day 1. Subjects will be instructed to take difluprednate QID for 4 weeks, followed by TID for 2 weeks,

followed by BID for 2 weeks, and finally QD for 2 weeks. This regimen can be modified or prolonged at the discretion of the investigator should signs of inflammation occur.

If any new or recurrent intraocular inflammation is observed, treatment and additional assessments should be collected to fully characterize inflammation location and severity. Treatment with topical difluprednate should be initiated at Q2 hour. The current study protocol details any further changes in steroid intervention when intraocular inflammation is observed.

Starting at Week 8, subjects will receive rescue aflibercept (2 mg IVT) and continue rescue aflibercept pro re nata (PRN) as needed 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 supplemental aflibercept treatment unless there is 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.

This is a double-masked study. 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 [redacted] for additional details. Safety and disease activity assessment will be performed by a masked physician. An independent review of OCT images, fluorescein angiography (FA) and fundus photographs, will be performed at a central reading center (masked to treatment assignment) to provide an objective graded assessment of these images.

An independent Data Monitor Committee (DMC) is set up to monitor the safety data periodically according to the DMC charter and study conduct on an ongoing basis. In addition to the ongoing masked review of the safety data, an interim analysis of efficacy and safety data is planned when all subjects have been followed for 24 weeks.

Unmasking of subject treatment assignments was planned to be reserved until the end of the study. However, emergency unmasking for all subjects has occurred, as determined by the Sponsor with input

from the Data Monitoring Committee, to preserve subject safety following a SUSAR event for one subject. The study in effect has thus become an open-label study, in which all prior masked subjects and clinic site staff will be able to continue study participation in an unmasked manner.

4.2. Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Table 1.1 and Table 1.2.
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 intraocular inflammation (protocol Section 5.11) and schedule of assessments. Additional assessment requirements may be reduced based on severity and location of the inflammation on any subsequent follow-up visits.

Study visits will be referred to in all tables and listings as the expected study day / study week corresponding to the protocol-defined time point for the visit.

5. Study Treatments

5.1. Randomization

Subjects will be randomized to the following treatment arms in Table 2.

Table 2: Study Arms

Arm	N	Day 1 IVT Injection	Day 8 ADVM-022 Dose (vg/eye)	Label for the Arm
1	6	Aflibercept	6×10^{11}	Aflib + 6E11
2	6	Sham	6×10^{11}	Sham + 6E11
3	6	Aflibercept	2×10^{11}	Aflib + 2E11
4	7	Sham	2×10^{11}	Sham + 2E11
5	9	Aflibercept	Sham	Aflib Only

For some analyses, the arms receiving ADVM-022 will be pooled at the dose level: 6E11 (Pooled) and 2E11 (Pooled).

5.2. Masking and Unmasking

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.

6. Sample Size and Power Considerations

The durability of ADVM-022 will primarily be assessed through evaluation of the need for rescue aflibercept (2mg IVT) due to worsening of DME disease activity. Disease activity and rescue aflibercept (2mg 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 (e.g., 24, or 48, or 96 weeks) when the true rate is 90% for the Control and 20% for the ADVM-022 treated. Table 3 summarizes the powers for the same hypothesis tests under several different assumptions in the rate of receiving any aflibercept injection.

Table 3: 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.

[f] 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).

7. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRFs) supplied by [redacted] or provided through electronic transfers from central laboratories and Central Reading Center. Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate through Week 96/EOS, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and the clinical contract research organization (if applicable) [redacted]

All final analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to [redacted] standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate [redacted] and Sponsor personnel.
- Protocol deviations have been identified and status defined (not CSR reportable/CSR reportable deviations).
- Analysis populations have been determined.

8. 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.

The following analysis populations are defined in this study:

8.1. Enrolled Population

Enrolled population is defined as all subjects who sign the informed consent form (ICF).

8.2. Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population is defined as all subjects who are randomized to treatment. Subjects will be analyzed according to the treatment they were assigned to as randomized, regardless of the treatment actually received.

8.3. Modified ITT (mITT) Population

The modified ITT (mITT) population is defined as all randomized subjects receiving study treatment at both Day 1 (aflibercept or sham) and Day 8 (ADVM-022 or Sham). Subjects will be analyzed according to the treatment they were assigned to as randomized. All efficacy analyses will be performed upon the mITT population.

8.4. Safety Population

Safety population will include all randomized subjects receiving study treatment at both Day 1 (aflibercept or sham) and Day 8 (ADVM-022 or Sham). Subjects will be analyzed according to the ADVM-022 they actually received on Day 8 and IVT aflibercept received on Day 1. All safety analysis will be performed upon the safety population.

8.5. Per-Protocol (PP) Population

The Per-Protocol Population (PP) includes all mITT subjects without major protocol violations/deviations. The list of major protocol violations/deviations will be identified and specified prior to final database lock for the trial that would lead to exclusion for the PP analysis. Efficacy analyses will also be conducted on the PP Population according to the treatment sequence group to which the subjects were randomized.

Summaries on PP population may potentially be omitted due to the small N's. The impact of critical intercurrent events (e.g., the steroid usage beyond the protocol defined regimen) on the outcome measures will be explored via some statistical models as sensitivity analyses.

9. General Statistical Considerations

No formal statistical testing is planned for the study. Descriptive summary by treatment arm will be provided for all safety and efficacy variables. Mean, standard deviation (SD), median and range will be provided for continuous variables; and frequency counts and percentages will be provided for categorical variables.

9.1. Unit of Analysis

For measurements taken at the subject level, the unit of analysis will be the individual subject and for measurements taken at the eye level, the unit of analysis will be the individual eye (study eye vs fellow eye) unless otherwise indicated.

Unless otherwise specified, eye-level summaries/measurements mentioned here hence refer to those for the study eye.

9.1.1. Study Eye

Only one eye will be selected as the study eye for the duration of the study. If both eyes meet all of the inclusion/exclusion criteria, the eye with the worse BCVA will be the study eye.

9.2. Missing or Inconclusive Data Handling

In general, only data observed for a given parameter or visit will be included in analyses and no missing data will be imputed.

9.3. Definition of Baseline

Baseline values are defined as the last available value prior to Day 1 treatment (aflibercept or Sham). For assessments measured both pre-dose and post-dose at Day 1 of the study, only measurements from the pre-dose time point are eligible for consideration as baseline.

9.4. Data Analysis Conventions

All final data analysis will be performed by [redacted] after the study is completed and the database has been locked. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables, listings, and figures using landscape orientation. All study data will be listed and sorted by subject, treatment, visit (as applicable), and eye (as applicable) based on all subjects in the Enrolled Population, unless otherwise specified.

Summaries by visit will include the Baseline value and post-Baseline visits based on planned assessment schedule. That is, only data from scheduled visits will be reported in table and figure summaries. Data from unscheduled assessments will be included in subject data listings only. The Baseline value will be flagged for the BCVA and SD-OCT listings, and Day 1 assessments will identify Pre-Dose versus Post-Dose.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two decimal places. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e, XX.X%). Change from Baseline will be calculated as follow-up visit minus Baseline.

Confidence intervals of the means and percentages will be provided at both 90% and 95% levels. P-values will be provided for between-group comparisons. 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 model 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.

Unless otherwise specified, summaries will be presented by treatment arm, all treatment arms combined, and, where appropriate, visit and eye.

Any measurements collected at an Early Termination Visit, if not allocated to a protocol-defined collection time point within the database, will be analyzed according to the nearest planned collection time point for the given assessment, and be analyzed according to the next planned collection time point for the given assessment only when the nearest planned collection time point already has assessments. Data from other assessments collected outside a permitted visit window will be recorded as a protocol deviation and unscheduled assessments will not be mapped to scheduled timepoint for any by-timepoint summary but will be included in subject data listings.

A derived study day will be computed for inclusion in subject data listings to identify the relative timing of visit/assessment dates, defined as the number of days relative to the aflibercept IVT or Sham ocular injection date (reference date) and calculated as:

Post-treatment study day = (Visit [or assessment] date – reference date) + 1.

Pre-treatment study day = (Visit [or assessment] date – reference date).

An IMP Relative Day will be provided in the listings as appropriated, when the reference date refers to the date of ADVM-022 administration.

The study day and IMP relative day will be computed for complete visit/assessment dates only and will be left missing in cases where a date is only partially available or entirely unknown.

For analysis of BCVA and CST as assessed by SD-OCT, an additional “last visit” time point will be derived for each parameter as the last available non-missing post-Baseline value for each subject and eye.

9.5. Adjustments for Multiplicity

No formal testing for efficacy will be performed. Therefore, no adjustments for multiple testing are planned.

10. Disposition of Subjects

Disposition of subjects will be summarized for all enrolled subjects (by treatment arm and for all) as follows:

- number of All Enrolled Subjects, Screen Failed Subjects by reason, number of subjects in ITT, MITT, PP, and Safety populations
- number and percentage of subjects completing the study and subjects discontinuing early from the study by reason as defined in protocol section 6.5
- number and percentage of subjects by reason for early study discontinuation

- number and percentage of subjects last visit completed
- number of subjects completed Aflibercept/Eylea (or Sham) Administration on Day 1
- number of subjects completed ADVM-022 (or sham) Administration on Day 8

Percentages above will be calculated using the total number of subjects assigned to each respective treatment group as the denominator for all percentages, unless otherwise specified.

A subject listing of treatment arm, dose, informed consent date with protocol version used for consent, completion indicator with study completion or discontinuation date, last completed visit, and the date and reason for premature study discontinuation will be provided.

A subject listing of Aflibercept/Eylea (or Sham) Administration on Day 1 and ADVM-022 (or sham) Administration on Day 8 will be provided.

Protocol deviations will be classified as major or minor based on a review of each protocol deviation by the project lead biostatistician, project medical monitor and Sponsor representative prior to the closure of the database. A significant protocol deviation (i.e., a major 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. Protocol deviations that are not major will be classified as minor. The number and percentage of subjects with any protocol deviations, any major protocol deviations, and any minor protocol deviations will also be tabulated as part of subject disposition. A subject listing will be provided which includes the date of the deviation, the deviation category, the deviation description, and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusion from each of the analysis populations.

11. Demographic and Pretreatment Variables

11.1. Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity, iris color and study eye (OD or OS). Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the ITT, mITT, PP, and Safety population.

Age (years) will be summarized using continuous descriptive statistics and will be reported in years and calculated using the following formula:

Age = (Informed consent date – Date of birth + 1) / 365.25 truncated as an integer

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, and ethnicity.

A subject listing that includes all demographic variables will be provided.

11.2. Pretreatment Variables

Pretreatment variables including which eye (OD/OS) is the study eye will be summarized by treatment arm for the Safety Population.

Date of initial DME diagnosis will be recorded within disease medical history and time since DME diagnosis will be calculated as the number of weeks from diagnosis date until informed consent date, as follows:

Time since DME diagnosis= (Informed consent date – Diagnosis date + 1) / 7

In case of partial diagnosis date, dates will be set to the first day of the month. Diagnosis date will be imputed as January 1 in case of missing day and month value. If year is not reported, time since diagnosis will be set to missing.

Other DME medical history will be summarized including DME Eye(s) Affected (OD/OS/OU), Time since Diabetes Diagnosis (in years), Type of Diabetes, and Number of Prior Anti-VEGF Injections (0, 1, 2, >2). Time since DME diagnosis, and Number of Prior Anti-VEGF Injections will be summarized for Study eye/Fellow eye.

Baseline BCVA and anatomical variables such as central subfield thickness (CST), total macular volume (mm^3), interretinal and subretinal fluid (IRF/SRF), and Diabetic Retinopathy Severity Scale DRSS score (Staurenghi et al 2018) will be summarized by treatment arm and for all subjects as part of more detailed data presentations. Baseline lab values of neutralizing antibodies (Nabs), HbA1c (%), and HLA-B27 status will be summarized as well.

Summaries of prior anti-VEGF treatment prior to enrollment are described in Section 0.

12. Medical History and Medication Usage

12.1. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 25.1 (or higher) and WhoDrug September 2022.

Ocular medical history is a subset of the overall medical history. Ocular medical history consists of those medical history records where the location field on the medical history eCRF is marked as location being oculus dexter (OD – right eye), oculus sinister (OS – left eye), or oculus uterque (OU – both eyes).

Listings of medical history will be generated for the combined ocular and non-ocular data.

Summary of the ocular medical history by SOC/PT for the study eye will be generated.

12.2. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO DD), Global, B3, September 2020 version (or higher), and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] Level 4 classification) and preferred name. If the ATC Level 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (eg, multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of “Uncoded.”

Prior medications/procedures are defined as those medications/procedures with a start date before injection of protocol-mandated IVT injection or sham on Day 1. Concomitant medications/procedures are defined as those that are in use at the time of IVT injection on Day 1 or started after dosing but prior to study completion/discontinuation. With this definition, it should be noted it is possible for a medication/procedure to be both a prior and a concomitant medication. Prior medication, concomitant medication, prior procedures and concomitant procedures will be summarized separately.

Ocular medications are a subset of the overall medications and consist of those medication records where the location field on the eCRF is marked as location being OD, OS, or OU. Concomitant medications for ocular pressure lowering will be summarized.

Listings of prior and concomitant medications (excluding anti-VEGF medications) will be generated for the combined ocular and non-ocular data. Listings of prior and concomitant procedures will also be listed together. Prior and concomitant anti-VEGF medications will be provided in a listing separate from other ocular medications.

12.2.1. Prior and Concomitant Anti-VEGF Intravitreal Injections

The number of prior and concomitant (i.e. within 30 days of study Day 1 and after) anti-VEGF intravitreal injections will be summarized for the study eye and fellow eye separately in the safety population based on the following time intervals:

- Total number of anti-VEGF injections since initial diagnosis of DME and prior to Day 1

A frequency distribution based on categorical outcome for each usage metric will be presented by treatment arm and for all subjects. This information will also be provided in a subject-level listing.

Of note, the supplemental aflibercept injections received in the study eye per the protocol defined rescue criteria will also be summarized as efficacy outcome measures (see Section 14.4).

12.2.2. Concomitant Topical Corticosteroid Use in the Study Eye

Topical corticosteroid medications are used to prevent inflammation post the study treatment and to manage recurrent inflammation during the study. The concomitant topical corticosteroid difluprednate usage in the study eye will be summarized. Starting on the date of study treatment on Day 1 until the later of the last visit date and the end date of last eye drop use for the study eye, each subject's daily number of corticosteroid difluprednate eye drops will be derived based on the start/end dates and frequency of each usage record: with 0 drops for not-using, 0.5 drops for QOD (every other day) in frequency, 1 drop for QD, 2 drops for BID, 3 drops for TID, 4 drops for QID, 5 drops for Q4H (every 4 hours, adjusting for the sleeping time of 8 hours), 9 drops for Q2H (every 2 hours) and 17 drops for QH (every hour). The following protocol is used for the recurrent intraocular inflammation treatment: if any new or recurrent intraocular inflammation is observed, treatment with topical difluprednate should be initiated at Q2 hour. Topical difluprednate at Q2 hourly should be utilized even in the absence of clinical signs of inflammation in cases with evidence of developing hypotony (IOP <10 mmHg). Weekly average of the daily number of eye drops will be calculated for each subject, i.e., average over each 7- day interval: 1-7 days, 8-14 days, 15-21 days and so on. Treatment with topical difluprednate beyond day 71 will be regarded as for management of intraocular inflammation or low IOP. The weekly average number of daily corticosteroid eye drops will be summarized by treatment arm, for each of the ADVM-022 dose group, and for all subjects.

In cases where cells persist for 2 weeks despite Q2 hourly difluprednate, in the absence of contraindications, intravitreal steroid, Ozurdex preferred, should be utilized as second-line steroid management for persistent inflammation (anterior or posterior) despite intensive regimen of topical difluprednate. Intravitreal steroid implant, Ozurdex preferred, should be utilized in cases with evidence of developing hypotony (IOP <10 mmHg) and persistent inflammation of any type. Subjects with the

usage of intravitreal steroid will be listed with the management indication of whether for intraocular inflammation or IOP.

12.3. Concomitant Medical Procedures

Any concomitant medical procedures will be listed by subject for the Enrolled Population.

13. Dosing Compliance and Treatment Exposure

As there is only a single dose of investigational study medication administered in this study, treatment exposure and compliance will not be summarized. Details of the administration of each subject's required study medication (prednisone, aflibercept, and ADVM-022) will be included within subject data listings.

14. Efficacy Analyses

Efficacy analysis endpoints will be evaluated, and descriptive statistics will be calculated in aggregate and by treatment arm, and by visit (when applicable). In addition, the summary by ADVM-022 dose group will be also provided for all efficacy endpoints. Efficacy analyses will include all subjects in the mITT population. The efficacy of ADVM-022 in the treatment of DME will be assessed by the following measures.

14.1. Time to Worsening of DME Disease Activity in the Study Eye

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

- An increase in CST > 50 µm as assessed by SD-OCT compared to the lower (Reference Value) 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 (Reference Value) of the two BCVA measurements recorded at Day 1 or Week 4

Time to a loss of > 5 letters in BCVA or an increase in CST > 50 µm due to worsening DME disease activity will be analyzed based on Kaplan-Meier statistical methods for the study eye through Week 96/EOS, including graphical display of the survival curves. Summarization will be done by treatment arm and will also be provided for each of the ADVM-022 dose groups. Subjects will be considered to have an event at the date where a loss of > 5 letters in BCVA or an increase in CST > 50 µm first occurred after the Reference Value date that could be either Day 1 or Week 4, and number of weeks to the event will be relative to the Study Treatment dosing date on Day 1 (Reference date). Time to the event or duration is calculated (and rounded to 1 decimal place) as:

Duration = ((event date or censor date – Reference date) + 1)/7.

Subjects who do not have any post-Reference Value date (Day 1 or Week 4) loss of > 5 letters in BCVA or an increase in CST > 50 µm will be censored at the date of study exit or the date of the subject's most recent visit prior to clinical data cut-off for any interim analysis.

When a Reference Value date is Day 1, any post-Day 1 worsening is an event. When Reference Value date is Week 4, any post-Week 4 worsening is an event; the prior to Week 4 occurrence of either an increase in CST > 50 µm or a loss of > 5 letters in BCVA compared to the Reference Value on Week 4 is not considered an event. The reference date is Day 1 regardless of the Reference Value date (Day 1 or Week 4).

14.2. Visual Acuity (ETDRS)

Visual acuity (VA) measurements will be measured at a starting distance of 4 meters, prior to dilating eyes. Vision will be assessed primarily through BCVA expressed as an ETDRS score (number of letters correctly read). If BCVA is equal to 0, light perception (LP), detection of hand movement (HM), and ability to count fingers (CF) will also be assessed. Visual acuity will be assessed at each visit in both eyes. In the event of a 30+ letters decrease in BCVA from Baseline, a follow-up BCVA assessment will be conducted after 1 hour. In this situation, the result from the repeat assessment will be used for analysis.

The observed and change from Baseline BCVA (based on number of ETDRS letters read) will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics and both 90% and 95% CIs by visit (including the derived 'last visit' time point) for each treatment arm and for all subjects dosed with ADVM-022. There will be 3 separate displays for summary descriptive statistics, one with scheduled visits, one with unscheduled visits, and one that includes both. For the interim analysis, summary tables will be done only for scheduled visits and listings will display all scheduled and unscheduled visits. Interim analysis will not include the derived 'last visit' time point. Mixed-effect models for repeated measures (MMRM) will be employed to explore the treatment effect on the change over time in BCVA on scheduled visits. The model will include effects for time, treatment, and the time by treatment interaction as fixed effects, and the baseline BCVA value as a covariate. Treatment comparisons and LS Mean (+/- standard error) values at each time point will be provided. An unstructured correlation matrix (UN) will be used to model additional autocorrelation within subject. If this model fails to converge, a Heterogeneous Toeplitz (TOEPH) structure will be used to model correlation between time points from the same subject. If both UN and TOEPH models fail to converge, a Heterogeneous Autoregressive(1) (ARH (1)) structure will be used to model correlation between time points from the same subject. If the UN, the TOEPH, and the ARH (1) models all fail to converge, then an Autoregressive(1) (AR (1)) structure will be used. In ARH (1) and AR (1) models, subject will be included as a random effect. Contrasts will be used to obtain estimates of the treatment differences at

each post-randomization visit. Point estimates with two-sided 90% and 95% CIs will be produced for each treatment difference.

The number and percent of eyes meeting each response definition specified above will be summarized for each eye and by treatment arm. In addition, the frequency distribution of change from baseline in BCVA at each visit will be provided with the change scores segmented to the following categories: lost >= 30 letters, lost 29 to 15 letters, lost 14 to 10 letters, lost 9 to 5 letters, lost 4 to 1 letters, no change (0), gained 1-4 letters, gained 5-9 letters, gained 10-14 letters, gained 15-29 letters, gained >= 30 letters.

Observed value and change from Baseline in BCVA values over time will be displayed graphically with mean +/- SE by treatment arm at each visit assessed. There will be 3 separate graphical displays, one with scheduled visits, one with unscheduled visits, and one that includes both. Graphs will also be produced showing the time course in individual subjects. Study eye and Fellow eye will be presented separately in summary tables while graphs will be for study eye only.

A subject listing of BCVA will also be produced. This listing will identify the baseline BCVA value, and flag values corresponding to decreases of 15 or more letters from baseline and decreases of 30 or more letters from baseline.

Manifest refraction information for each eye will be listed.

14.3. Spectral Domain Ocular Coherence Tomography

Central subfield thickness – Spectral Domain Ocular Coherence Tomography (SD-OCT) will be performed using approved equipment and standard techniques to evaluate thickness and fluid compared to Baseline values. SD-OCT will be conducted on the study eye at all visits, and for the fellow eye at Screening and Week 96 Visit or EOS. Imaging will be performed prior to administering aflibercept at any scheduled visits.

Endpoints will include central subfield thickness and macular volume and be assessed by the Central Reading Center.

The following parameters will be assessed by the Central Reading Center and summarized in tables:

- Retinal thickness (µm) and macular volume (mm^3)
    - Central subfield thickness (CST [µm]), applies only to retinal thickness summary
    - Total macular volume (mm^3), applies only to macular volume summary

The following additional SD-OCT endpoints will be summarized in tables:

- The number and percentage of subjects with CST <300 µm over time through Week 96
- The number and percentage of subjects with intraretinal fluid (IRF)
- The number and percentage of subjects with subretinal fluid (SRF)

Baseline value for all parameters will be last available value prior to Day 1 treatment (aflibercept or Sham).
For continuous outcomes, a similar MMRM analysis to that described in section 14.2 will be applied. They will also be displayed graphically over time in a similar manner as described in section 14.2.

Categorical outcomes will be summarized by eye using counts and percentages for each treatment arm and for all subjects at each visit, including the derived 'last visit' time point. Percentages will be based on the number of subjects in each treatment arm with responses.

Subject listings of SD-OCT will also be produced divided into separate listings for each of the groups of parameters specified above.

14.4. Rescue Aflibercept Usage

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

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, 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 is given by the medical monitor.
Information on administration and retreatment criteria will be provided in a subject-level listing.

Aflibercept rescue injections will be summarized by visit through 96 weeks, per subject for the study eye, with the following variables:

- The proportion of subjects requiring a rescue aflibercept IVT injection at any time, along with the total number of injections per subject.

- The proportion of subjects who do not require a rescue aflibercept IVT injection at any time.
- Injection rate per 365 days, defined as number of rescue aflibercept injections received by all subjects (cumulative number of aflibercept injections) divided by the sum of total at risk duration days across all subjects (i.e., the sum of the number of days observed from week 8 until each subject's end of study or through a certain visit (e.g., week 12, week 16, etc.)), multiplied by 365.25. Specifically:
- $\frac{\text{Number of rescue aflibercept injections received by all subjects}}{\text{Sum of total at risk duration across all subjects}} \times 365.25$
- Time to first rescue aflibercept requirement

Number of injections per subject will be summarized with descriptive statistics as a ordinal outcome, and injection rates will be summarized as a continuous outcome with descriptive statistics and both 90% and 95% CIs. Summarization will be by treatment arm and for all subjects. Mean cumulative function (MCF) curve over time will be plotted for the mean cumulative number of injections.

Count of recurrent rescue aflibercept administration following treatment with ADVM-022 will be analyzed using Negative Binomial regression for recurrent events. Treatments will be compared adjusting for baseline BCVA and CST. The logarithm of time at risk of experiencing a rescue aflibercept administration will be used as an offset variable in the model. Time to first rescue aflibercept requirement will be analyzed use Cox proportional hazards regression given the proportional hazards assumption is fulfilled.

14.5. Other Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed with the following procedures:

- For each timepoint, DRSS will be determined by the Central Reading Center using ultra-wide field color fundus photography and compared to Baseline.
- 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.

14.6. Digital Color Fundus Photography (CFP)

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.

For each timepoint, DRSS will be determined by the Central Reading Center using ultra-wide field color fundus photography and compared to Baseline.

DRSS levels are (*cf*. Staurenghi et al, 2018):

- DR Absent (Level 10)
- Microaneurysms Only (Level 20)
- Mild NPDR (Level 35)
- Moderate NPDR (Level 43)
- Moderately Severe NPDR (Level 47)
- Severe NPDR (Level 53)
- Mild PDR (Level 61)
- Moderate PDR (Level 65)
- High-Risk PDR (Level 71)
- High-Risk PDR (Level 75)
- Advanced PDR (Level 81)
- Advanced PDR (Level 85)
- Cannot Grade For Levels 81 Or 85 (Level 90)
- Cannot Determine

The following parameters will be assessed:

- 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

The number and percentage of subjects with 2-step and 3-step improvement in DRSS score over time through Week 96/EOS, and number and percentage of subjects with 2-step and 3-step worsening in DRSS score over time through Week 96, will be tabulated for the study eye by visit for each treatment arm and for all subjects. The treatment effect on DRSS changes over time will be explored using generalized mixed models for categorical outcomes. Specifically, defining 2-step improvement as recurrent events, similarly for 3-step improvement, 2-step worsening, and 3-step worsening, the incidence of such events will be analyzed using negative binomial regression. Treatments will be compared adjusting for baseline BCVA and CST. The logarithm of time at risk of experiencing an event will be used as an offset variable in the model.

A subject listing of the color fundus photography grading parameters will also be produced.

14.7. Vision Threatening Complications

Vision threatening complications (anterior segment neovascularization, diabetic macular edema, high-risk PDR development, vitreous hemorrhage, or tractional retinal detachment) are determined by

ultra-wide field imaging and clinical examination by the Investigator. Vision threatening complications data will come from EDC exam details, AE reports and Central reading Center interpretation of images. Development of vision threatening complications will be summarized and listed.

14.8. Fluorescein Angiography

Ultra-wide field Fluorescein Angiography (FA) will be conducted in the study eye post-Baseline at Weeks 12, 24, 68 and 80, and will be conducted in both eyes at Screening, Week 48 and Week 96/EOS. The following parameters will be assessed:

- Presence or absence of leakage of FA dye

Presence or absence of subretinal hemorrhage also will be summarized. Shift tables will be provided comparing each follow-up visit to Baseline for both eyes (study eye and fellow eye), based on the count and percentage of subjects in each shift category. All reported results will be included within subject data listings, however the shift table will exclude any results which are reported as 'cannot determine'.

A subject listing of the fluorescein angiography grading parameters will also be produced.

15. Safety Analyses

All safety analyses described in following sections will be conducted using the Safety Population and will be analyzed according to the dose received/treatment arm assignment.

15.1. Adverse Events

An adverse event (AE) is defined by protocol as any untoward medical occurrence in an enrolled subject regardless of its causal relationship to the investigational medicinal product. The Investigator or site staff is to be responsible for detecting, documenting, and reporting all events that meet the definition of an AE or a serious adverse event (SAE), regardless of relationship to study treatment.

All AEs reported or observed during the study are to be recorded on the AE eCRF. Information to be collected includes event term; location; date and time of onset; Investigator assessment of seriousness, severity, and relationship to each of the specific study treatment/procedure: ADVM-022/Sham, aflibercept/Sham, difluprednate regimen, and IVT; date and time of resolution of the event; any required treatment or evaluations; outcome; and whether the adverse event is an adverse event of special interest. An adverse event of special interest will be reported 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)

An AE resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must be reported. MedDRA version 25.1 or later 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.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the day and time ADVM-022 treatment is initiated. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

Ocular AEs are a subset of AEs and are identified as those AEs where the location field on the AE eCRF is marked as OD, OS, or OU. In general, summaries of ocular AEs will be similarly summarized at the subject level for study eye and non-study eye separately.

The relationship of each AE to the ADVM-022/Sham, aflibercept/Sham, IVT, or the difluprednate regimen should be determined by the Investigator using these explanations:

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

For analysis purposes, AEs considered related to each of the specific study treatment/procedure (per Investigator) will include AEs with relationship equal to likely related or definitely related. Not related

AEs will include AEs with relationship equal to not related or unlikely related. In the event relationship is not specified, the event will be summarized as related.

An overall summary will be presented for both eyes (study eye and fellow eye) that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment arm and for all subjects. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye and fellow eye separately) or non-ocular, treatment-related TEAEs, serious TEAEs, TEAEs by maximum severity, TEAEs leading to early study discontinuation, TEAEs leading to death.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC) and preferred term (PT). Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment arm and for all subjects at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level for study eye and fellow eye separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be counted once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC. The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC and PT for the following: maximal severity and suspected relationship to each of the specific study treatment/procedure.

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.

If the severity is not reported, the event will be summarized as severe unless there is other information indicating the event was life-threatening or fatal. To count the number of subjects with any TEAEs by maximal severity, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity. However, when tabulating the total number of TEAEs by maximal severity for a subject, all TEAEs reported by the subject at the maximal severity that are coded to the same PT and SOC will be counted.

Separate summaries will be provided for the following categories of AEs:

- Overall Summary of Adverse Events
- Ocular TEAEs (separately for study eye and fellow eye)

- Non-ocular TEAEs
- Serious ocular TEAEs (separately for study eye and fellow eye)
- Serious non-ocular TEAEs
- TEAEs by Severity (separately for study eye, fellow eye and non-ocular)
- TEAEs by Relationship to Study Treatment Medication (separately for study eye, fellow eye, and non-ocular)
- Ocular TEAEs of Special Interest defined as sight-threatening adverse events, as reported by the Investigator (separately for study eye and fellow eye)
- Ocular TEAEs Related to Study Treatment Medication (separately for study eye and fellow eye)
- Ocular TEAEs Related to IVT Injection Procedure Per Investigator (separately for study eye and fellow eye)
- Ocular TEAEs Related to Aflibercept Injection Per Investigator (separately for study eye and fellow eye)
- Ocular TEAEs Related to Difluprednate Use Per Investigator (separately for study eye and fellow eye)
- TEAEs Leading to Discontinuation of Study Drug (separately for study eye, fellow eye, and non-ocular)

Separate listings of AEs will be produced to list all AEs, all SAEs, and AEs leading to treatment withdrawal and death. Study day, as well as IMP Relative Day will be included in all listings.

15.2. Intraocular Pressure (IOP)

The IOP measurements will be performed using a Goldmann applanation tonometer or Tono-pen™, as specified in the protocol 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 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 IOP values and changes from Baseline for each eye (study eye and fellow eye) will be summarized using continuous descriptive statistics by visit (including the last observed visit) and eye for each cohort and for all subjects. Additionally, the frequency and percentage of participants with IOP (mmHg) between 0-5, 6-7, 8-10, 11-15, 16-20, 21-25, 26-30, and >30 will be summarized. Also, the frequency

and percentage of participants with increases and decreases from baseline in IOP by at least 5 mmHg, 10 mmHg, and 15 mmHg will be reported at each visit, at any visit, and at the last visit.

A subject listing of IOP will also be produced.

15.3. Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the eyelids, conjunctiva, cornea, lens, iris, and anterior chamber will be performed at each visit. The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). Anterior chamber cells will be graded as 0, 0.5+, 1+, 2+, 3+, or 4+, and anterior chamber flare will be graded as 0, 1+, 2+, 3+, or 4+.

Shift tables will be provided for each eye (study eye and fellow eye) for all slit-lamp biomicroscopy parameters except anterior chamber cells and anterior chamber flares comparing each follow-up visit to Baseline by treatment based on the count and percentage of subjects in each shift category. The shift from baseline categories will include the following categories for the given assessment: No Change, Normal to Abnormal (CS or NCS), \ or Abnormal (CS or NCS) to Normal. Additionally, the number and percentage with shifts at any visit and the last visit will also be reported.

The anterior chamber cells and anterior chamber flare grades will be treated as continuous variables and will be summarized by treatment arm and visit with descriptive statistics: the number of non-missing values, mean, standard deviation, median, minimum, and maximum.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

15.4. Indirect Ophthalmic Examination

The dilated indirect ophthalmoscopy examination will be conducted at each visit in both eyes and include an evaluation of posterior segment abnormalities of the vitreous, peripheral retina, macula, choroid, and optic nerve. 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. Fundus hemorrhage is graded as 0, 1+, 2+, or 3+, VC cells is graded as 0, 0.5, 1+, 2+, 3+, or 4+, and haze is also assessed with possible scores of 0, 0.5+, 1+, 2+, 3+, 4+, or 5+. 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.

Shift tables for categorical indirect ophthalmic parameters will be summarized for each eye (study eye and fellow eye) comparing each follow-up visit to Baseline based on count and percentage of subjects

in each shift category, by treatment and for all subjects. Additionally, the number and percentage with shifts at any visit and the last visit will also be reported.

Fundus hemorrhage, VC cells and VC haze grades will be treated as continuous variables and will be summarized by treatment arm and visit with descriptive statistics: the number of non-missing values, mean, standard deviation, median, minimum, and maximum.

A subject listing will also be produced.

15.5. Physical Examination

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.

The physical examination results for each body system, graded as normal or abnormal (NCS or CS), as well as height, weight, and body mass index (BMI) information, will only be listed by subject.

15.6. Vital Signs

Vital signs will consist of blood pressure, pulse rate, body temperature, and respiratory rate. Blood pressure, pulse, respiration rate and body temperature will be measured at Screening and at all visits including Week 96/EOS /Early Termination visit. Vital signs should be obtained sitting after resting for a minimum of 5 minutes.

Each vital sign assessment will be summarized with continuous descriptive statistics by visit and treatment arm and for all subjects. Change from Baseline will also be summarized to each post-Baseline visit.

A subject listing of the vital signs results will also be produced.

15.7. ECG Evaluation

A 12-lead Electrocardiogram (ECG) will be taken for each subject at Screening (which serves as the Baseline assessment) 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, and these

assessments will be summarized using descriptive statistics by treatment arm and for all subjects at each visit.

Shifts from Baseline to EOS/or Early Termination Visit in the overall results of the ECG (normal, abnormal NCS, abnormal CS) will also be tabulated by cohort and for all subjects. The following shift from baseline categories will be reported: No Change, Normal to Abnormal (CS or NCS), Abnormal (CS or NCS) to Normal.

A subject listing of the ECG results will also be produced.

15.8. Laboratory Tests

Clinical Laboratory and 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. Results of the laboratory tests will be summarized descriptively in Tables by visit and treatment arm and for all subjects. A subject listing for each of the laboratory tests will also be produced. Aqueous and vitreous humor sample analyses for aflibercept concentration are optional and, if available, will be displayed separately in a Listing.

15.8.1. Clinical Laboratory Data

Summarization of clinical laboratory data will be based on results provided by the central laboratory. In the event that sites use local laboratory results (e.g., to confirm study eligibility on expedited basis), those results will not be included within the data analyses unless they are added to the study database.

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

Laboratory values and normal ranges will be presented and summarized using conventional units. Each parameter will be summarized by treatment arm and for all subjects with continuous descriptive statistics. Change from Baseline will also be summarized by treatment arm and for all subjects. For each test, the minimum and maximum post-Baseline values across all visits, along with the changes from Baseline, will be summarized.

For all parameters where a normal range is defined, shift from Baseline category to post-Baseline category at each time point will also be tabulated. Abnormal labs will be defined as any labs where the lab value falls outside of the normal range (where a normal range is defined). The following shift from baseline categories will be reported: No Change, Normal to Abnormal, Abnormal to Normal.

Clinical laboratory data will be provided in subject-level listings. These listings will include sex and age to assist in clinical interpretation.

15.8.2. Vector Expression and Immune Response Analytical Assays

Subjects' samples (both blood and/or aqueous humor) will be collected to measure the following:

- Total Antibodies to AAV.7m8: serum for total anti-AAV.7m8 antibodies will be measured in an [redacted]
- Neutralizing Antibodies to AAV.7m8: serum for neutralizing anti-AAV.7m8 antibodies will be measured [redacted]
- Anti-Aflibercept Antibodies: serum for the humoral immune response against aflibercept will be measured in an [redacted]
- Aflibercept Protein Expression: Serum and aqueous humor samples will be collected for the presence of aflibercept protein to be measured [redacted]
- Cell-Mediated Immune Response: cellular immunity against AAV.7m8 capsid and aflibercept protein will be measured in an [redacted]

Anti-AAV.7m8 antibody will be summarized by visit, and by treatment arm and dose level (6E11, 2E11, aflibercept only) with number and proportion of values at each titer level.

Neutralizing antibody titer levels will be summarized by visit, and by treatment arm and dose level (6E11, 2E11, aflibercept only) with the number and proportion of subjects at a lower titer level (<1:125) and higher titer level (≥1:125) at each visit.

Anti-aflibercept antibodies will be summarized by visit, and by treatment arm and dose level (6E11, 2E11, aflibercept only) with number and proportion of values at each titer level.

Protein expression will be summarized by visit, and by treatment arm and dose level (6E11, 2E11, aflibercept only) with continuous descriptive statistics based on change from baseline for the $\log_{10}$ concentrations (mg/dL) of the ADVM-022 Aflibercept Protein Expression data from the serum and aqueous samples.

Cell-Mediated Immune Response will be summarized in a manner similar to Anti-AAV.7m8 antibody.

Note that the titer level will be set to 0 for negative or not applicable antibody results. Concentrations for protein expression levels that are below the limit of quantification (BLQ) will be set to one-half of the lower limit of quantification. Concentrations will be set to missing for assays that are not obtained or have insufficient volume.

A subject listing will also be produced.

15.9. Pregnancy Testing

Serum pregnancy test will be performed at Screening for females of child-bearing potential only. Urine pregnancy test will be performed locally at Screening Visit, on Day 1 with negative results confirmed prior to dosing, and monthly thereafter.

Serum pregnancy test results from central lab and urine pregnancy test results from local labs will be listed only.

16. Interim Analyses

Ongoing reviews of safety data as well as dose-escalation recommendations will be performed by the DMC. The outputs to be provided for review by the DMC are beyond the scope of this SAP.

An interim analysis (IA) is planned after all subjects have completed the Week 24 visit or withdrawn from the study earlier. Tables and listings to be provided for the interim analysis are a subset of those described in the protocol ADVM-022-04 [redacted] to be completed at Week 96/EOS study visit according to this SAP. The selected tables, listings and figures for the interim analysis are annotated in Section 16.1.

A data cutoff date will be defined in conjunction with such interim analysis, and analyses where an end date is required (e.g., duration of an event, time 'at risk' for event rates) will be as of the cutoff date.

17. Changes from Protocol-Stated Analyses

The changes from the protocol-slated analyses are as follows:

[redacted] analyses will also be conducted based on the following categories for [redacted] in [redacted]

- [redacted] or more from Baseline
  - Yes indicates a negative effect for subjects and
  - No indicates the subject maintained their vision or their vision improved.
- [redacted] or more from Baseline
  - Yes indicates a positive effect for subjects and
  - No indicates the subjects maintained their vision or their vision worsened.

[redacted] will be carried out for by dose level (6E11, 2E11, none) comparison of number and proportion of BCVA changes from Baseline at each visit, in terms of decrease of [redacted] and [redacted] or [redacted] and [redacted]

[redacted] will be carried out by dose level (6E11, 2E11, none) comparison of number and proportion of subjects [redacted]

18. References

Staurenghi G, Feltgen N, Arnold JJ, et al. Impact of baseline Diabetic Retinopathy Severity Scale scores on visual outcomes in the VIVID-DME and VISTA-DME studies. Br J Ophthalmol 2018; 10(7):954-958

19. Revision History

19.1. Amendment 1

Updates for added clarifications which do not impact the analysis are not listed below, otherwise the following updates were made:

Section	Description of Change	Rationale
1	Protocol version changed to Amendment 7.0	Update to current version of protocol
14.1	Refined language and bullet points on BCVA-event analysis	Updated language to better coincide with IA 2 BCVA table updates. Updates occurred to provide a more complete picture of which subjects are in which category and to clarify category meaning.
16	Added clarifications on the immunology and protein expression data and categories that will be reported in tables.	Updated based on what is actually collected.

ADVM-022-04: Changes to Planned Analyses Described in SAP v2.0
Prepared by: [redacted]
Date: January 29, 2024
Revised by: [redacted]
Revision Date: April 26, 2024
Revised by: [redacted]
Revision Date: June 11, 2024

<table>
<tr><th>SAP Section</th><th>Summary of Changes</th></tr>
<tr><td>5.1 Table 2</td><td>Updated the labels for Treatment Arm

Labels from Table 2 in SAP:
<table>
<tr><th>Arm</th><th>N</th><th>Day 1
IVT Injection</th><th>Day 8
ADVM-022 Dose
(vg/eye)</th><th>Label for the Arm</th></tr>
<tr><td>1</td><td>6</td><td>Aflibercept</td><td>6×10^{11}</td><td>Aflib + 6E11</td></tr>
<tr><td>2</td><td>6</td><td>Sham</td><td>6×10^{11}</td><td>Sham + 6E11</td></tr>
<tr><td>3</td><td>6</td><td>Aflibercept</td><td>2×10^{11}</td><td>Aflib + 2E11</td></tr>
<tr><td>4</td><td>7</td><td>Sham</td><td>2×10^{11}</td><td>Sham + 2E11</td></tr>
<tr><td>5</td><td>9</td><td>Aflibercept</td><td>Sham</td><td>Aflib Only</td></tr>
</table>
Updated Labels:
<table>
<tr><th>Arm</th><th>N</th><th>Day 1
IVT Injection</th><th>Day 8
ADVM-022 Dose
(vg/eye)</th><th>Label for the Arm</th></tr>
<tr><td>1</td><td>6</td><td>Aflibercept</td><td>6×10^{11}</td><td>Arm 1: Aflibercept + $6x10^{11}$</td></tr>
<tr><td>2</td><td>6</td><td>Sham</td><td>6×10^{11}</td><td>Arm 2: Sham + $6x10^{11}$</td></tr>
<tr><td>3</td><td>6</td><td>Aflibercept</td><td>2×10^{11}</td><td>Arm 3: Aflibercept + $2x10^{11}$</td></tr>
<tr><td>4</td><td>7</td><td>Sham</td><td>2×10^{11}</td><td>Arm 4: Sham + $2x10^{11}$</td></tr>
<tr><td>5</td><td>9</td><td>Aflibercept</td><td>Sham</td><td>Arm 5: Aflibercept + Sham</td></tr>
</table></td></tr>
<tr><td>Section 8.3</td><td>Updated the definition for mITT Population:

SAP Definition:

The modified ITT (mITT) population is defined as all randomized subjects receiving study treatment at both Day 1 (aflibercept or sham) and Day 8 (ADVM-022 or Sham). Subjects will be analyzed according to the treatment they were assigned to as randomized. All efficacy analyses will be performed upon the mITT population.

Modified Definition:

The modified ITT (mITT) population is defined as all randomized subjects receiving study treatment at both Day 1 (aflibercept or sham) and Day 8 (ADVM-022 or Sham). Subjects will be analyzed</td></tr>
</table>

	according to the *study treatments they actually received on Days 1 and 8*. All efficacy analyses will be performed upon the mITT population.
Section 8.4	Updated the definition for Safety Population: SAP Definition: Safety population will include all randomized subjects receiving study treatment at both Day 1 (aflibercept or sham) and Day 8 (ADVM-022 or Sham). Subjects will be analyzed according to the ADVM-022 they actually received on Day 8 and IVT aflibercept received on Day 1. All safety analysis will be performed upon the safety population. Modified Definition: Safety population will include all randomized subjects who received *any study treatment on Day 1 (aflibercept or sham).* Subjects will be analyzed according to the study treatments they actually received on Days 1 and 8. All safety analysis will be performed upon the safety population. All safety analysis will be performed upon the safety population. Note that there were two subjects (randomized to Aflibercept + $6x10^{11}$ and Aflibercept + Sham) who received treatment on Day 1, but the Sponsor discontinued the subjects and they did not receive treatment on Day 8. These subjects are included the safety summaries and are summarized in the "Aflibercept + No Treatment group".
Section 8.5	No analyses were run using the Per Protocol population due to a low number of subjects in Per Protocol Population.
Section 9.4	Updated to include Quartile 1 (Q1) and Quartile 3 (Q3) for summaries of continuous outcomes.
Section 14 (Multiple Sections)	All efficacy tables were summarized by treatment group and the following 2 pooled dose groups: ADVM-022 $6x10^{11}$ (Pooled) and ADVM-022 $2x10^{11}$ (Pooled).
Section 14.4 and Table 14.2.4.1.1	Updated derivation of the Injection Rate per 365 days to derive for each subject, and to use 'from day 8' to calculate the at-risk duration. **SAP Derivation:** Injection rate per 365 days, defined as number of rescue aflibercept injections received by all subjects (cumulative number of aflibercept injections) divided by the sum of total at risk duration days across all subjects (i.e., the sum of the number of days observed from week 8 until each subject's end of study or through a certain visit (e.g., week 12, week 16, etc.)), multiplied by 365.25. Specifically: (Number of rescue aflibercept injections received by all subjects" /"Sum of total at risk duration across all subjects" ×365.25) **Modified Derivation:**

	Injection rate per 365 days calculated *for each subject* is defined as number of rescue aflibercept injections received *by that subject* (cumulative number of aflibercept injections) divided by the sum of total at risk duration days *for that subjects* (i.e., the sum of the number of days observed from *day 8* until the subjects end of study or through a certain visit (e.g., week 12, week 16, etc.)), multiplied by 365.25. Specifically: (Number of rescue aflibercept injections ~~received by all subjects~~" /"Sum of total at risk duration ~~across all subjects~~" ×365.25) The subject specific injection rates per 365 days were summarized as a continuous outcome using mean, 90% CI and 95% CI. Table 14.2.4.1.1 was updated to summarize the average years of follow up rather than total years of follow up.
Section 15.1 and Tables 14.4.x	Updated all AE summaries to include all AEs instead of TEAEs (defined as any event that occurs or worsens on or after the day and time ADVM-022 treatment is initiated). Additional updates to AE summary tables: • Added severity to the following tables: o Table 14.4.1.1.1 o Table 14.4.1.3.1.1 o Table 14.4.1.3.2 o Table 14.4.1.4.1.1 o Table 14.4.1.5.1.1 o Table 14.4.1.7.1 • Updated Table 14.4.1.3.1.1 to exclude AESIs • Added number of events to all AE summary tables
Table 14.1.1	Split the planned 14.1.1 disposition tables into two separate tables: • Table 14.1.1 - Subject Disposition All Enrolled Subjects • Table 14.1.2 - Screen Failures Screen Failed Subjects
Tables 14.2.5.3.1, 14.2.5.4.1, and 14.2.5.5.1	For the summaries of Incidence of 3-Step or Greater Improvement in Diabetic Retinopathy Severity Scale (DRSS) Score Over Time Through Week 96, Incidence of 2-Step or Greater Worsening in Diabetic Retinopathy Severity Scale (DRSS) Score Over Time Through Week 96, and Incidence of 3-Step or Greater Worsening in Diabetic Retinopathy Severity Scale (DRSS) Score Over Time Through Week 96, adjusted rates, rate ratios, and rate difference were not estimated and not included in the table due to too few events occurring across treatment groups.
Tables 14.5.2.1.1 and 14.5.3.1.1	Updated the shift categories to include: • Abnormal (NCS) to Abnormal (CS) • Abnormal (CS) to Abnormal (NCS) • Normal to Abnormal (CS) • Normal or Abnormal (NCS) to Abnormal (CS)

Multiple TFL Outputs	Updates made to titles, column headers, labels, and footnotes for consistency across outputs. Added dose columns for multiple TFLs.
Added Table 14.2.6.1.1	Table added to assess secondary outcome of Vision Threatening Complications
Additional Figures	Figures by dose groups added: Figure 14.2.1.2; Figure 14.2.2.1.2; Figure 14.2.2.2.2; Figure 14.2.3.1.2; Figure 14.2.3.2.2; and Figure 14.2.4.1.2
Additional Listings	Listings added: Listing 16.2.4.2; Listing 14.2.3; Listing 14.2.5; Listing 16.2.8.9
Tables 14.4.1.6.3.1 and 14.4.1.6.4	These tables are no longer applicable. Tables 14.4.1.2.1.1 and 14.4.1.2.2 include events by severity

Appendices Containing Statistical Confidential Information

(Statistical Programming Shells)

Intentionally Removed from Published Version