Statistical Analysis Plan

A Phase 2 Study to Evaluate the Safety and Treatment Effect of Intravitreal AVD-104 in Participants with Diabetic Macular Edema

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Protocol Details:

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[redacted]

1 INTRODUCTION

Protocol Number: AVD-104-C301

Protocol Title: A Phase 2 Study to Evaluate the Safety, and Treatment Effect of Intravitreal AVD-104 in Participants with Diabetic Macular Edema (DME).

Rationale: To determine the safety and preliminary efficacy of intravitreal injections of AVD-104, a novel glyco-mimetic nanoparticle, in reducing macular edema associated with diabetic retinopathy.

1.1 Trial Objectives

Primary Objective:

- Evaluate the safety and tolerability of AVD-104 in participants with DME.

Secondary Objectives:

- Evaluate the treatment effect of AVD-104 at multiple doses on central subfield thickness (CST) as measured by Spectral-domain optical coherence tomography (SD-OCT).
- Evaluate the treatment effect of AVD-104 at multiple doses on Best-corrected visual acuity (BCVA) using ETDRS (Early-Treatment Diabetic Retinopathy Study) visual acuity charts.

Exploratory Objective:

- [redacted]

2 STUDY DESIGN

2.1 Trial rationale and Description of the Design

The trial will be a multi-center, randomized evaluation of the effect of AV-104 in participants with diabetic macular edema. Participants will undergo baseline examinations to include BCVA, slit lamp and indirect ophthalmoscopy, both spectral domain OCT and OCT angiography, and ultrawide-field fluorescein angiography analysis.

For all potential participants, eligibility based on severity of diabetic retinopathy must be confirmed by the central reading center prior to participant enrollment. In addition, all screening laboratory tests must be performed, and the results must be evaluated and determined to be acceptable by the investigator prior to participant enrollment into the study.

Participants will then be randomized to one of two different groups:

- Group 1: Two (2) injections of high-dose AVD-104 [redacted]
- Group 2: Three (3) injections of low-dose AVD-104 [redacted].

Participants will be carefully monitored over the next [redacted] days with repeat evaluations to ascertain any effect from AVD-104. Specific rescue criteria will allow the participants to be treated with the current standard-of-care agents should there be any significant decline in their vision.

The end of the study is defined as the date of the last visit of the last participant in the study.

The trial is designed to provide initial efficacy data for AVD-104 in participants with DR. The parameters evaluated will include change in vision, change in CST on OCT, [redacted]

2.2 Subject Randomization

The randomization module of the Merative Zelta EDC system will be used to assign participants to one of two different groups as noted in Section 2.1 above.

The reading center and masked vision examiner will be masked to the participants randomization and personal information in the trial.

2.3 Sample Size Estimation

There will be a planned enrollment up to thirty (30) participants in the trial. [redacted]

2.4 Objectives and Endpoints

Objective	Endpoint
Primary	
Evaluate the safety and tolerability of AVD-104 in participants with DME.	Ocular and clinical examinations of participants for any evidence of ocular, systemic, or serious adverse events.
Secondary	
Evaluate the treatment effect of AVD-104 at multiple doses on central subfield thickness (CST) as measured by Spectral-domain optical coherence.	Change in CST as measured by SD-OCT at Month 1, 2, and 3.
Evaluate the treatment effect of AVD-104 at multiple doses on Best-corrected visual acuity (BCVA) using ETDRS ((Early-Treatment Diabetic Retinopathy Study) visual acuity charts.	Change from baseline in BCVA as assessed with the ETDRS visual acuity) at Month 1, 2, and 3.
Exploratory	
[redacted]	[redacted]

2.5 Handling of Missing, Incomplete, and Repeat Data

No data imputation will be performed.

2.6 Statistical Methodology

Data analysis will be based on safety population. In general, the data will be presented as data listings. However, summary statistics will be presented for selected variables. For continuous variables, data will be summarized using descriptive statistics, including n, mean, standard deviation, median, min and max. The categorical variables will be summarized using n, frequency and percent.

3 STUDY POPULATION

3.1 Definitions of Subject Populations

Participants will be 18 years or older with evidence of DME secondary to DR and no history of neovascularization in the study eye. There will be no racial or sex limitations. For purposes of analysis, the following populations are defined:

Population	Description
Safety	All randomized participants received at least one (1) dose of study treatment. Participants will be analyzed according to the treatment they actually received.

All tables will be run using the Safety population, and all data will be included in data listings

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3.2 Screening and Enrollment

Screen failures are defined as candidates for enrollment who consent to participate in the clinical study but are not subsequently randomized/entered in the study or included in the analysis population due to anatomic or medical issues.

Rescreening Criteria:

- [redacted]

3.3 Population Demography

Data will be analyzed by treatment group, demographic characteristics, and demographic subgroups.

3.4 Disease Diagnosis and Prior Treatment

The Investigator will attempt to establish diagnosis of disease and any events based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis, not the individual signs/symptoms will be documented. Prior treatment will be documented and tabulated.

3.5 Disposition of Study Participants

Data will be presented by treatment group indicating number and percentage of Total Enrolled, Screen Failures, Randomized, Treated, Completed Study, and Early Discontinuation (due to Withdrew Consent, Adverse Events, Investigator Decision, Lost to Follow-Up, or Death).

3.6 Protocol Deviations

Protocol Deviations will be recorded in the Merative Zelta EDC system along with all other study data. They will be categorized and included in the final tables and listings.

[redacted]

4 EFFICACY ANALYSES

All efficacy data will be presented as data listings except visual acuity and retinal thickness (as by OCT assessed) The data for these variables will be summarized using summary statistics by scheduled visit for each treatment group.

5 SAFETY ANALYSES

All safety analyses will be performed using the Safety Population.

The primary safety variable is the incidence and severity of ocular and systemic AEs and SAEs. MedDRA Version 26.1 (September 2023) nomenclature will be used to code adverse events. The number and percent of participants reporting ocular and systemic AEs/SAEs will be tabulated based on the MedDRA System Organ Class and Preferred Term. Summary tables will be generated for all AEs regardless of causality as well as for treatment-related AEs.

[redacted]

The following safety data will be analyzed and presented in tabular format:

- Overview of Treatment Emergent Adverse Events
- Summary of Adverse Events by System Organ Class and Preferred Term
- [redacted]

5.1 Adverse Events

The definitions of an Adverse Event (AE) and Serious Adverse Event (SAE) – as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports - can be found in Appendix 4 of the Study Protocol.

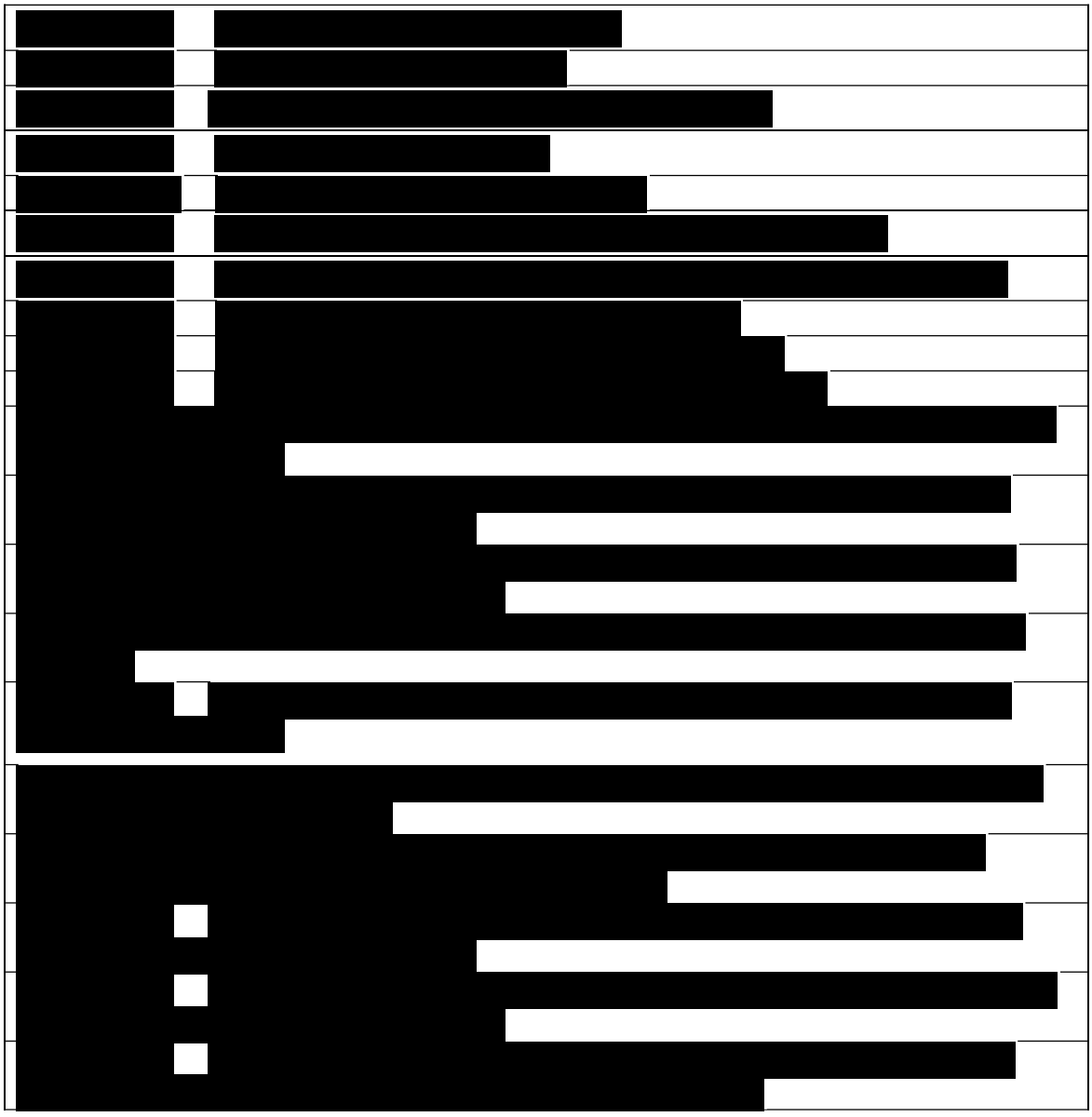
All AEs and SAEs will be collected from the start of treatment until the final follow-up visit at the time points specified in the SoA (Section 2 of Study Protocol).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) and will be tabulated accordingly.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 35 days after the last dose. Abnormal pregnancy

outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be tabulated accordingly.

6 [redacted]



7 [redacted]