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

Protocol Number: AVD-104-C301

Version [redacted]

Compound Number: AVD-104

Sponsor Name and Legal Registered Address: Aviceda Therapeutics, Inc.

One Broadway, Cambridge, MA. 02142, USA

[redacted]

Approval Date:

[redacted]

[redacted]

Date

NCT number: NCT06181227

Date: 25 SEP 2023

PROTOCOL APPROVAL – PRINCIPAL INVESTIGATOR SIGNATURE

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Version [redacted]

Version Date: [redacted]

I have read the protocol described above. I agree to conduct the study as described in the protocol. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) and all applicable national and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board or Independent Ethics Committee (IRB/IEC) and any other institutional requirements. These are stated in “Guidance for Good Clinical Practice” International Council for Harmonisation (ICH) guideline E6(R1) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and any other applicable regulatory requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB/IEC.

Principal Investigator: _____

Print Name of Investigator: _____

Date: _____

TABLE OF CONTENTS

LIST OF TABLES

1. SYNOPSIS

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.

Objectives and Endpoints:

Objective	Endpoint
Primary	
Evaluate the safety and tolerability of AVD-104 in participants with DME	1. Ocular and clinical examinations of participants for any evidence of ocular, systemic adverse 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 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	1. Change in CST as measured by SD-OCT at Month 1, 2, and 3 2. Change from baseline in BCVA as assessed with the ETDRS visual acuity at Month 1, 2, and 3
Exploratory	
- [redacted]	1. [redacted]

Overall Design: Participants will have evidence of DME secondary to diabetic retinopathy that meets the inclusion criteria.

The primary objective is to evaluate the tolerability and treatment effect of intravitreal injections of AVD-104 in participants with DME. Participants will receive either three injections of low-dose AVD-104 [redacted] each 28 days apart or two intravitreal injections of AVD-104 at a dose of [redacted] (high-dose) 56 days apart. Serial SD-OCT, UWFA, and OCT-A will be performed to evaluate the treatment effect on central subfield thickness (CST) and areas of non-perfusion. All participants will be followed-up for safety until day 84.

Number of Participants:

There will be a planned enrollment up to 30 participants. This will potentially require up to [redacted] screenings.

Treatment Groups and Duration:

One group will receive three injections of low-dose AVD-104 [redacted] each 28 days apart. The second group will receive two injections of high dose AVD-104 [redacted] 56 days apart. Both groups will be followed for 84 days after injection.

2. SCHEDULE OF ACTIVITIES (SOA)

Activity	Screen	Baseline					
		Predose	Dose	Post Dose			
Day/month	**Day -28 to -1**	**Day 0**			**Day 28**	**Day 56**	**Day 84**
Window (±days)					**±7**	**±7**	**±7**
Informed Consent/HIPAA	X						
Eligibility Criteria	X	X					
Medical History	X						
Ocular History[1]	X						
Demographics[2]	X						
Review adverse events/ocular symptoms[3]		X		X	X	X	X
Record TEAEs				X	X	X	X
Vital signs[4]	X	X			X	X	X
Brief Physical examination[5]		X					X
Urine/Serum Pregnancy Test[6]	X	X			X	X	X
Prior/Con Medications	X	X			X	X	X
Central Labs[7]	X						X
BCVA by ETDRS[8]	OU	OU			SE	SE	OU
Slit Lamp Biomicroscopy	OU	OU			SE	SE	OU
IOP	OU	OU		SE	SE	SE	OU
Indirect Ophthalmoscopy	OU	OU			SE	SE	OU
SD-OCT	OU	OU			SE	SE	OU
OCT-A		OU			SE	SE	OU
Color fundus photographs	OU						OU
Fluorescein angiogram		OU			SE		OU
Select/Confirm Study Eye		X					
IVT injection high-dose group (n=15)			SE			SE	

Activity	Screen	Baseline					
		Predose	Dose	Post Dose			
Day/month	**Day -28 to -1**	**Day 0**			**Day 28**	**Day 56**	**Day 84**
Window (±days)					**±7**	**±7**	**±7**
IVT injection low-dose group (n=15)			SE		SE	SE	

Abbreviations AST = BCVA = best-corrected visual acuity; Con = concomitant; ETDRS = early-treatment diabetic retinopathy study; HIPPA = Health Insurance Portability and Accountability Act; IOP = intraocular pressure; IVT = intravitreal injection; OCT-A = Optical coherence tomographic angiography ; SD-OCT = spectral-domain optical coherence tomography; TEAE = treatment emergent adverse event; OU = Both eyes; SE = Study eye

1. Ocular history shall include but is not limited to diabetic retinopathy-related events (hemorrhage, previous laser, etc.), eye involvement, and localization (central versus non-central).
2. Demographics include age, gender, race, ethnicity, height, and weight.
3. The severity of ocular symptoms (burning/stinging, itching, foreign body, discomfort, dryness, photophobia, and pain) shall be evaluated on a visual analogue scale of 0 to10.
4. Vital signs include temperature (oral, tympanic, or temporal), resting heart rate, and blood pressure.
5. Brief physical examination includes appearance, mood, and affect only. Physical examination for symptom driven findings may be conducted at any time during the study.
6. Urine pregnancy tests shall be performed in females of childbearing potential only. The high and low dose groups will be tested at screening, baseline, day 56, and day 84 or termination. The low dose group will be retested again at day 28 before their second injection. If the test is positive at any of these timepoints, then a confirmatory serum pregnancy test must be conducted.
7. Central labs consist of complete blood count and metabolic profile as outlined in Appendix 2.
8. Best-corrected visual acuity measured using Early Treatment of Diabetic Retinopathy Study protocol.

3. INTRODUCTION

Diabetic retinopathy is the leading cause of vision loss in working individuals and diabetic macular edema and macular ischemia are two of the major contributors to this morbidity. (Ixcamey 2021; Ting 2016). Despite the widespread use of intravitreal anti-VEGF agents and steroids, there is still a large unmet medical need in this population (Haritoglou 2020; Sadiq 2020). A significant percentage of patients with DME do not respond completely to anti-VEGF therapy (Bressler 2016; Felfeli 2019). Approximately 30% of patients treated with the most effective agent, faricimab, still have edema present at 24 weeks (Sahni 2019). The use of anti-VEGF and anti-Ang 2 agents targets specific pathways associated with increased vascular permeability and neovascularization but does not target up-stream causes of progressive diabetic retinopathy. Although VEGF has been identified as one of the key factors, other inflammatory mediators such as MCP-1, TNF-**α**, and IL-6 are upregulated in patients with chronic DME (Kwon 2018). In addition, adhesion molecules including VCAM-1, ICAM-1, and E selectin are correlated with the progression of diabetic complications (Derosa 2016, Rajab 2015, Xu 2023).

An understanding of the role of other inflammatory factors in DME will help elucidate why anti-VEGF alone fails to resolve DME in many patients and why diabetic retinal ischemia persists. The activation and retinal leukostasis of neutrophils in the development of macular ischemia and retinal endothelial damage has been scientifically characterized for decades.(McLeod, Lefer et al. 1995) VEGF alone has been shown to cause neutrophil chemoattraction, leukocyte plugging, retinal edema and ischemia in a non-human primate model. (Tolentino, Miller 1996, Hofman, Blaauwgeers 2000) However, when VEGF was withdrawn in this model, leukocyte plugging, and edema did not resolve (Tolentino unpublished observation). This observation predicted the current situation of refractory macular edema and ischemia that is seen today with anti-VEGF agents. The persistence of macular edema and ischemia was due to neutrophil activation and ICAM-1 and CD18 mediated leukostasis. (Joussen, Murata et al. 2001). An optimal therapy for these refractory complications of diabetic retinopathy would be the deactivation or the elimination of these neutrophils in the retina and retinal vasculature coupled with elimination of the complement induced tight junction disruption and Selectin upregulation that captures and holds the leukocytes in retinal vascular stasis and maintains non-VEGF mediated vascular leakage.

The knowledge of how to modulate immune cells, like monocytes and neutrophils, has progressed to the point that therapeutic interventions can be evaluated. All immune cells have glycoproteins that reside on their cell surfaces called sialic acid binding immunoglobulin-type lectins, or Siglecs. Each cell type tends to have more of one or a few particular Siglecs that control its activity. (Gonzalez-Gil, 2021) Neutrophils, in general, have Siglec 9 present on their surfaces. These Siglec receptors activate an inhibitory pathway within the cell called immunoreceptor tyrosine-based inhibitory motif (ITIM). This is done through recruitment of the tyrosine phosphatase Src homology region 2 domain- containing phosphatase-1 (SHP-1). By activating these Siglec glycoproteins with an agonist, the neutrophils can be downregulated. AVD-104 is a novel glycan coated nanoparticle that is being developed as an intravitreal injection to treat diabetic retinopathy and its components. Its interaction with the Siglec 9 receptors present on neutrophils activates this inhibitory pathway, which leads not only to a

decrease in inflammatory mediators but the potential to induce programmed cell death in these hyperactivated neutrophils. (Chen, Bai et al. 2018)

Another inflammatory factor that causes a non-VEGF dependent disruption of retinal vascular endothelium is anaphylatoxin C3a. C3a is a complement factor that binds to vascular endothelium causing an intracellular mediated disruption of the blood retinal barrier and a weakening of vascular cadherin mediated vascular tight junctions. (Wu, Zou et al. 2016). C3a also stimulates the expression of E-selectin a major adhesion receptor that binds activated sialyl Lewis a and x bearing leukocytes. (Smith and Bertozzi 2021) Inhibition of complement pathway production of C3a would also be effective in restoring the non-VEGF disrupted tight junctions of the blood retinal barrier and a significant reduction of E-selectin. The constitutive inhibitor of the alternative complement cascade is complement factor H (CFH). Sialic acid molecules bind to CFH to activate the molecule and thereby inhibit the inflammatory complement cascade (Fearon 1978). AVD-104 binds sialic acid binding domains on CFH to similarly downregulate the complement pathway as reported in the Investigator's Brochure (IB).

The emergence of glycobiology and the ability to directly modulate both the activity of immune cells and the complement pathway has opened the opportunity to treat this recalcitrant form of diabetic retinopathy with a dual mechanism Siglec-9 agonist and complement inhibitor. In pulmonary literature, agonizing Siglec-9 with a rudimentary glyco-mimetic induced selective apoptosis in activated neutrophils (Chen 2018). AVD-104 while designed to target complement and Siglec 11, does bind and agonize Siglec-9 which is the main Siglec found on neutrophils and T Cells. The mechanism of resolving neutrophil and complement activation locally in the eye with AVD-104 has the potential to treat patients that failed anti-VEGF therapy and to treat macular ischemia; as of now, an untreatable and visually compromising complication of diabetes. This dual mechanism of action of AVD-104 – inhibition of activated neutrophils and down- regulation of the alternative complement system -- shows great promise in slowing the visual loss in diabetic retinopathy due to chronic inflammation.

3.1. Study rationale

Numerous studies now support the concept that abnormalities in the innate cellular immune system are causative agents in the pathophysiology of diabetic retinopathy (Xu 2017). Sialic acid binding immunoglobulin like receptors (Siglecs) are a target to affect an inhibitory mechanism to thereby downregulate immune cells, including neutrophils (Varki, 2022). AVD-104 binds to Siglec receptors to inhibit neutrophils and lower inflammatory cytokine production. It also enhances the action of complement factor H (CFH) to dampen the complement system. This dual mechanism of action of AVD-104 should be effective in treating the chronic inflammation present in diabetic retinopathy (DR). This study is designed to assess the treatment effect of this novel compound, which for the first time addresses the cellular component of diabetic retinopathy.

3.2. Background

Scott and team first reported the increased anti-inflammatory effect of sialic acid molecules when placed on nanoparticles and then presented to inflammatory cells with appropriate Siglec receptors (Spence, 2015). His experiments in a mouse sepsis model showed a remarkable down-regulation of inflammation using sialic acid coated nanoparticles compared to sialic acid

alone. [redacted] It has previously been shown that sialic acid molecules also have a direct effect on the complement cascade (Fearon, 1978). Sialic acid polymers also bind properdin and subsequently reduce the complement amplification pathways (Shahraz, 2022). These studies strongly support the potential role of a sialic acid mimetic in downregulating the innate immune system involved in inflammatory conditions like DR. In vitro studies using FACS analysis have demonstrated that 98% of blood derived neutrophils express Siglec 9. [redacted]

The unique dual mechanism of action of AVD-104 will be highlighted in the pre-clinical data presented in the IB. [redacted]

3.3. Benefit/risk assessment

The need for a therapy to significantly reduce the visual morbidity in DR is clear and, if accomplished, would provide great benefit to patients with progressive vision loss. The risk of intravitreal injections is relatively small and well characterized. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of AVD-104 may be found in the Investigator's Brochure.

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	
1. Evaluate the treatment effect of AVD-104 at multiple doses on central subfield thickness (CST) as measured by Spectral-domain optical coherence	3. Change in CST as measured by SD-OCT at Month 1, 2, and 3
2. 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	4. Change from baseline in BCVA as assessed with the ETDRS visual acuity) at Month 1, 2, and 3
Exploratory	
[redacted]	[redacted]

4.1. Study design

4.1.1. Overall 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.

Participants will then **be randomized to one of two different groups**. One group will receive three injections of low-dose AVD-104 [redacted] each 28 days apart. The second group will receive two injections of high-dose AVD-104 [redacted]

These are doses that have previously been shown to be safe in an ongoing trial in macular degeneration. They will then be carefully monitored over the next 84 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.

There will be a planned enrollment up to 30 participants in the trial. This will potentially require up to [redacted] screenings.

4.1.2. End of study definition

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

4.2. Scientific rationale for study design

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, or changes in perfusion of the macula or peripheral retina to see if AVD-104 has any effect on them.

4.3. Justification for dose

5. STUDY POPULATION

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.

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Willingness and the ability to provide signed informed consent as to the full nature and purpose of the study (includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol), acknowledging the possible risks of study procedures. Additionally, participants must provide Health Insurance Portability and Accountability Act (HIPAA) authorization.
2. ≥18 years old at the time of signed informed consent
3. Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging, and able to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment as determined by the Investigator
4. Male participants:
    - Males with female partners of childbearing potential must agree to use protocol-defined methods of contraception and agree to refrain from donating sperm for up to [redacted] after the last dose of study drug.
5. Female participants:
    - A female participant is eligible to participate if she is not pregnant (see Appendix 5), or breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP) as defined in Appendix 5 OR
    - A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least [redacted] after the last dose of study treatment].
6. Diagnosis of diabetes mellitus (type 1 or 2), as defined by the World Health Organization and/or American Diabetes Association
7. Decreased visual acuity (VA) due to DME, with BCVA letter score of 75−20 letters on ETDRS-like charts (20/32−20/320 Snellen equivalent)
8. DME represented by macular thickening on SD-OCT involving the center of the macula: CST ≥325 µm with Spectralis (Heidelberg Engineering Inc., Heidelberg, Germany) at screening or CST ≥315 µm for Cirrus (Carl Zeiss Meditec, Dublin, CA), CST ≥315 µm for Topcon (Tokyo, Japan), or CST ≥295 µm for Optovue (Fremont, CA) where Spectralis is unavailable.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

A. Presence of the following ocular conditions – in the Study Eye:

1. Any IVT anti-VEGF treatment within 3 months before randomization

2. Any use of Iluvien® (Alimera Sciences, Inc., Alpharetta, GA) in the last 3 years; or Ozurdex® (Abbvie, Chicago, IL) or Xipere (Bausch & Lomb, Vaughan, Ontario, Canada) in the last 6 months
3. Any history of pan-retinal photocoagulation (PRP) treatment
4. [redacted]
6. History of macular laser photocoagulation
7. [redacted]
9. Any signs of high-risk PDR, defined as:
    a. Any vitreous or preretinal hemorrhage
    b. Neovascularization of disc ≥1/3-disc area on clinical examination
    c. (Neovascularization elsewhere ≥1/2-disc area within an area equivalent to the standard mydriatic ETDRS 7-field on clinical examination)
10. [redacted]

B. [redacted]

6. [redacted]

5.2.1. Medical condition exclusions

1. [redacted]

5.2.2. Lifestyle restrictions

Meals and Dietary Restrictions

There are no dietary restrictions for participants.

Caffeine, Alcohol, and Tobacco

Participants will be encouraged to discontinue any tobacco use during the study and avoid excessive use of alcohol. Participants may continue to consume caffeine at their normal levels.

Activity

Participants must abstain from strenuous exercise for 1 hour after each injection.

5.3. Screen failures

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.

6. TREATMENTS

6.1. Treatments administered

Study Treatment Name:	AVD-104
Dosage formulations:	Group 1: [redacted]
	Group 2: [redacted]
Unit dose strength(s):	Group 1: [redacted]
	Group 2: [redacted]
Route of Administration	Intravitreal injection
Dosing instructions:	Group 1: Two injections 56 days apart
	Group 2: Three injections each 28 days apart
Packaging and Labelling	Study treatment will be provided in a sealed container as a frozen suspension.

6.2. Method of treatment assignment

A random number generator will be used to assign participants to one of two different groups.

6.3. Masking

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

6.4. Dose discontinuation

[redacted]

Refer to the SoA for data to be collected at the time of treatment discontinuation and subsequent follow-up, and, for any further evaluations that need to be completed.

6.5. Dose modification/interruption

[redacted]

6.6. Rescue criteria

[redacted]

[redacted]

6.7. Preparation/handling/storage/accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment material received and any discrepancies must be reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator along with delegated individuals is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.8. Concomitant therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9. Treatment after the end of the study

There will not be any study treatment after the end of the study.

6.10. Discontinuation from the study

The following criteria are to be used for discontinuation of participants from the study.

- [redacted]

6.11. Lost to follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- [redacted]

7. STUDY PROCEDURES

Only prospective participants as defined by the criteria in Sections 5.1 and Section 5.2 (inclusion/exclusion criteria) will be considered for entry into this study.

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. Screening laboratory tests may be repeated once at the discretion of the investigator or Aviceda.

A urine or serum pregnancy test administered to WOCBP at the baseline (day 1) visit must be negative prior to randomization.

A participant is considered to have entered the study at the time of enrollment to baseline (day 0).

7.1. Informed consent and patient privacy

The study will be fully discussed with the patient. Any patient wishing to participate must give informed consent prior to any study-related procedures are performed or there is a change in treatment. The patient must also give authorization (US only), data protection consent (Europe only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures are performed or there is a change in treatment.

Each patient who provides informed consent will be assigned a patient number that will be used on patient documentation throughout the study.

7.2. Visits and associated procedures

Evaluations should be performed by the same evaluator throughout the study whenever possible.

Unless otherwise specified, procedures are recommended to be done in the order listed.

Screening

- Obtain informed consent and authorization
- Review eligibility criteria
- Collect demographic information and medical and ophthalmic history
- Vital signs (blood pressure and pulse rate)
- Urine pregnancy test for women of childbearing potential (confirmed with serum if positive)
- Collect information about concomitant medications and procedures
- Collect blood for central labs
- Perform the following procedures in both eyes:
    - BCVA using ETDRS method following refraction
    - Full ophthalmic examination: slit lamp biomicroscopy, IOP assessment, and dilated indirect ophthalmoscopy examination
    - SD-OCT imaging

- Dilated ultra-wide field (UWF) color fundus photography
-

Baseline (Day 0)

- Review eligibility criteria and reading center confirmation of eligibility
- Query for ocular symptoms
- Vital signs (blood pressure and pulse rate)
- Brief physical exam
- Urine pregnancy test for women of childbearing potential (confirmed with serum if positive)
- Collect information about concomitant medications and procedures
- Perform the following procedures in both eyes:
  - BCVA using ETDRS method following refraction
  - Full ophthalmic examination: slit lamp biomicroscopy, IOP assessment, and dilated indirect ophthalmoscopy examination
  - SD-OCT imaging
  - OCT-A
  - Ultra wide-field fluorescein angiography

After completion of these procedures, and the participant still meets entry criteria, and the central reading center (CRC) has confirmed participant eligibility based on ocular inclusion/exclusion criteria from the screening visit, and the investigator has confirmed patient eligibility based on the results from the blood chemistry, hematology, and urine or serum pregnancy test from the screening visit; the participant will be enrolled

- Perform the following procedures in the study eye:
  - Administer assigned study medication
  - Conduct post-injection assessments at 30 minutes

Days 28, 56, and 84

- Query for adverse events and ocular symptoms
- Vital signs (blood pressure and pulse rate)
- Brief physical exam (month 3 only)
- Urine pregnancy test where indicated and positive results confirmed with serum test (low dose group at day 28 prior to second injection; both groups at month 3 only)
- Review concomitant medications and procedures
- Collect blood samples for central lab (month 3 only)
- Perform the following procedures in the study eye (both eyes at month 3)
  - BCVA using ETDRS method following refraction
  - full ophthalmic examination: slit lamp biomicroscopy, IOP assessment, and dilated indirect ophthalmoscopy examination
  - SD-OCT imaging
  - OCT-A
  - Dilated ultra-wide field (UWF) color fundus photography (both eyes at month 3 only)
  - UWF Fluorescein angiogram (month 1 and 3)
  - Administer assigned study medication at day 28 and 56 in low-dose group; day 56 in high dose group
  - Conduct post-injection assessment at 30 minutes

8. ADVERSE EVENTS

The definitions of an AE and SAE can be found in Appendix 4.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or other aspects of the study, or that caused the participant to discontinue the study treatment or other aspects of the study (see Section 9).

8.1. Time period and frequency for collecting AE and SAE information

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).

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).

All SAEs will be recorded and reported to the sponsor or designee within [redacted] as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within [redacted] of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be

reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4

8.2. Method of detecting AE and SAE

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3. Follow-up of AE and SAE

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs (as defined in Appendix 4), will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 6.11). Further information on follow-up procedures is given in Appendix 4.

8.3.1. Regulatory reporting requirements for SAE

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation.
- The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority (IRB)/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.2. Pregnancy

- 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 [redacted] after the last dose.
- If a pregnancy is reported, the investigator should inform [redacted] Medical Monitor and Aviceda within [redacted] of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.4. Treatment of overdose

N/A

8.5. Safety

8.5.1. General

Participants will be monitored for any safety and tolerability issues affecting any system.

Any significant abnormality in the opinion of the investigator noted on systemic values obtained from the clinical laboratory testing should be reported as possible adverse events. If there is any question that these represent serious abnormalities, both the medical monitor and sponsor should be notified.

8.5.2. Visual safety

For issues affecting vision. The following are guidelines for reporting the possible adverse events:

- [redacted]

[redacted]

8.5.3. Physical examinations

- A physical examination will include, at a minimum, assessments of appearance, mood, and affect. Height and weight will also be measured and recorded at screening.
- A brief physical examination will include, at a minimum, assessments of appearance, mood, and affect and symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.5.4. Vital signs

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be taken before blood collection for laboratory tests and after the participant has been sitting for 5 minutes. Repeat testing can be done if needed by the Investigator.

8.5.5. Clinical safety laboratory assessments

Any significant abnormality noted in systemic values obtained from the clinical laboratory testing (central laboratory) should be reported as possible adverse events. If there is any question that these represent serious abnormalities, both the medical monitor and sponsor should be notified.

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within [redacted] after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to
- normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If there is an urgent need and laboratory values from a non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.6. Health economics or medical resource utilization and health economics

[redacted]

9. [redacted]

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11. APPENDICES

Appendix 1. Abbreviations and trademarks

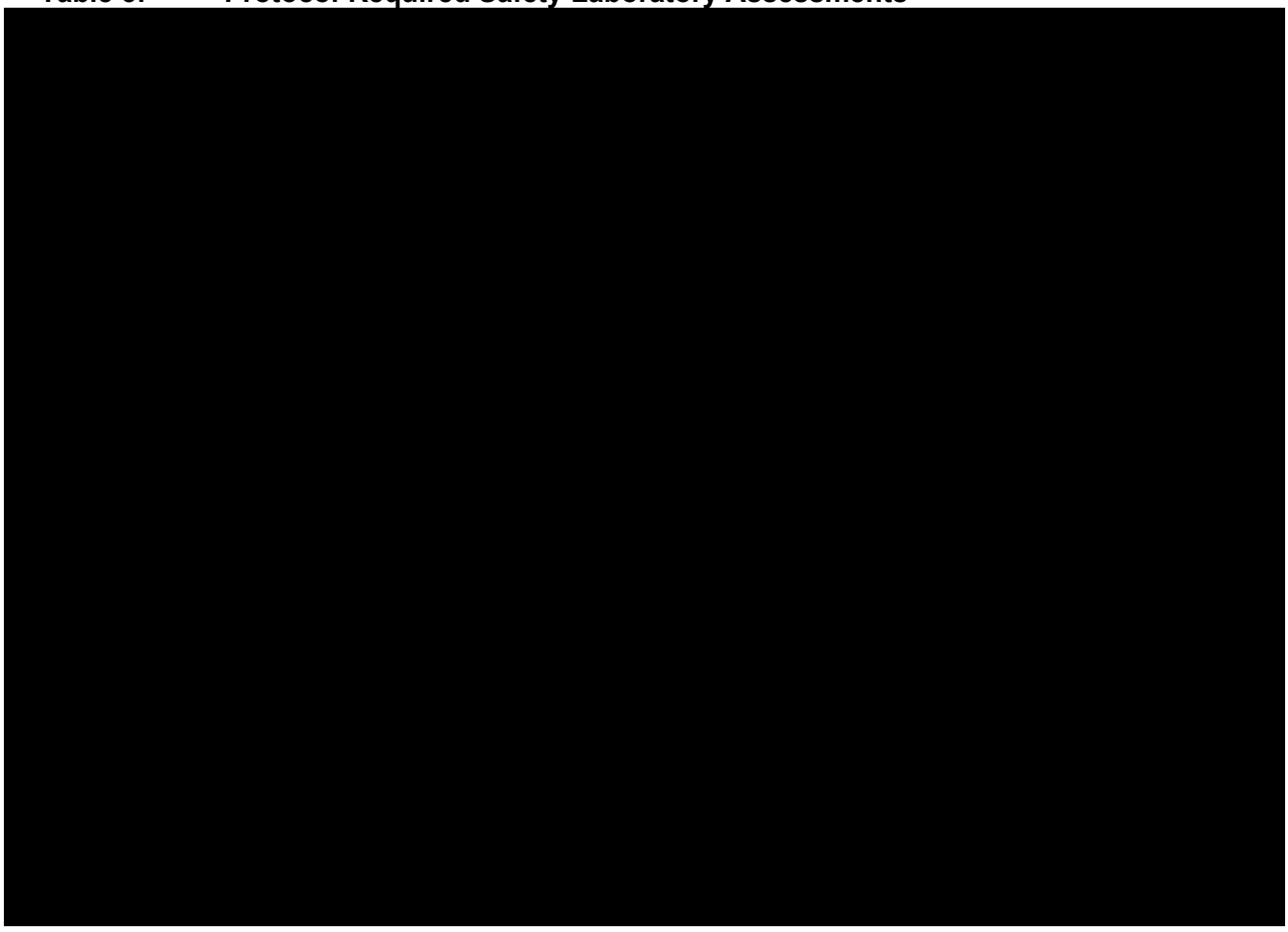
Term	Definition
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AMD	Age-related macular degeneration
AST	Aspartate Aminotransferase
AVD-104	PSA-PLGA-nanoparticle construct
BCVA	Best-Corrected Visual Acuity
BLD	Bright-light damage
C3	Complement 3
CATT	Comparison of Age-Related Macular Degeneration Treatments Trial
CFH	Complement factor H
CFI	Complement factor I
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CNV	Choroidal neovascularization
CRC	Central reading center
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DA	Disk area
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
DR	Diabetic retinopathy
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EIOP	Elevated intraocular pressure
EOM	Every other month
ERG	Electroretinogram
ETDRS	Early-Treatment Diabetic Retinopathy Study
EZ	Ellipsoid zone
FA	Fluorescein angiography
FAF	Fundus Autofluorescence
FSH	Follicle-stimulating hormone
F/U	Follow-up
GA	Geographic Atrophy
GCP	Good clinical practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form

Term	Definition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional review board
ITIM	Immunoreceptor tyrosine-based inhibitory motif
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVRS	Interactive Voice Response System
IVT	Intravitreal Injection
IWRS	Interactive Web Response System
MCH	Macrocytic anemia
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MIP-1	Macrophage inflammatory protein 1 A and B
MPO	Myeloperoxidase
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NET	Neutrophil extracellular trap
NHP	Non-human primate
OCT	Optical Coherence Tomography
PEG	Polyethylene glycol
PD	Pharmacodynamics
PLGA	Poly (D, L-lactic-co-glycolic acid)
PMA	Phorbol myristate acetate
PSA	Polysialic acid
q	Quisque (every)
ROS	Reactive oxygen species
RP2D	Recommended Phase 2 dosing
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SD-OCT	Spectral-Domain Optical Coherence Tomography
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SHP-1	Src homology region 2 domain-containing phosphatase-1
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
VA	Visual Acuity
VAS	Visual Acuity Scale
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WOCBP	Women of childbearing potential
YAG	Yttrium aluminum garnet

Appendix 2. Clinical laboratory tests

- The tests detailed in Table 3 will be performed by the central laboratory, except as noted below.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3: Protocol-Required Safety Laboratory Assessments



Appendix 3. Study governance considerations

Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed consent process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative, defined as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the clinical research, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

Both blood and aqueous humor samples will be kept in storage for a potential exploratory analysis regarding the pathogenesis of macular degeneration and response to study treatment.

Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period.

Data protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of clinical study data

Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study

is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Definition of what constitutes source data can be found in 21 CFR 312.62(b).

Study and site closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ophthalmic scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition includes either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or Clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the medical monitor in lieu of completion of the Sponsor's AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by the medical monitor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to safety team. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
Investigators assess or "grade" severity of each AE and SAE of their participants. The National Institutes of Health suggest a 5-scale rating to adequately capture the severity (NIH, 2017). The 5-scale rating consists of: mild, moderate, severe, life-threatening, death. The 5 point grading scale of mild/moderate/severe/life-threatening/death will be used for all adverse events. The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. • Life-threatening: An event that would indicate urgent intervention is required to prevent complete loss of vision or the eye • Death Adverse events are also coded using the Medical Dictionary for Regulatory Activities (MedDRA), which consists of highly specific standardized terminology that was developed by ICH to facilitate to adequately capture the important information needed to assess adverse events and help to assure participant safety and medical understanding of the event. Citation: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to [redacted]
- However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to** [redacted]
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor or Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide [redacted] with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within [redacted] of receipt of the information.

Reporting of SAE [redacted]

Appendix 5. Contraceptive guidance and collection of pregnancy information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonals highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the protocol-defined time frame:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for 3 months after study completion or from last dose
  - Female partner is using a highly effective contraceptive method
- Agree to use a male condom plus an additional method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential.
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- Refrain from donating sperm for duration of study and for 3 months from last dose of study drug.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulationb • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male* *sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence* *needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Female participants

Female participants of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table above.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine (dipstick or microscopy) pregnancy test
- Pregnancy testing urine testing will be performed at screening, M12, and M24. If the urine test is positive, it should be confirmed by serum testing.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of pregnancy information

Male participants with partners of reproductive potential who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within [redacted] of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor.
- Generally, follow-up will be no longer than [redacted] following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the sponsor within [redacted] of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy, which is considered reasonably related to the study treatment by the investigator, will be reported to the sponsor as described in Appendix 4 While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating:

- Will discontinue study treatment but not be withdrawn from the study