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|---|---|
| **Official Protocol Title:** | A 2-Part Study Consisting of An Open-Label Multiple Ascending Dose (MAD) Safety Study, and a Dose-Finding Single-Masked Comparative Safety and Preliminary Efficacy Study of Intravitreal (IVT) EYE103 in a Mixed Population of Participants With Diabetic Macular Edema (DME) and Neovascular Age-Related Macular Degeneration (NVAMD) |
| **NCT Number:** | NCT05919693 |
| **Document Date:** | 30-Oct-2023 |

# Summary of Changes Document

**Protocol Number: EYE103-101**

A 2-part study consisting of an open-label multiple ascending dose (MAD) safety study, and a dose-finding single-masked comparative safety and preliminary efficacy study of intravitreal (IVT) EYE103 in a mixed population of participants with diabetic macular edema (DME) and neovascular age-related macular degeneration (NVAMD)

**Previous Version Number and Amendment Date:** Version 3.0, 12 OCT 2023
**New Version Number and Amendment Date:** Version 3.1, 30 OCT 2023

This amendment, dated 30th October 2023, makes the following changes to Version 3.0 of the protocol (dated 12 October 2023). The major changes (updated in several sections of the protocol) and rationale are summarized below, with specific details provided in Table 1. Text that is added is in bold and deleted text has a strikethrough in Table 1. In the tracked change version of the protocol, new/changed text is bolded, and deleted text has a strikethrough.

The changes provided in Version 3.1 of the protocol are primarily to capture early signs of efficacy in the dose-finding phase of the study

| | |
|---|---|
| Change: | This version permits participants at up to 5 selected sites to elect to receive 3 additional study treatments. |
| Rationale: | Data from Part 1 of the study shows a good safety profile in the participants treated to date and supports the safety of treating participants for longer |

Protocol changes are detailed in Table 1 with accompanying rationale and justification. Where identical changes were made to the Protocol Synopsis and the text in the full Protocol, only the change to the Protocol Synopsis is shown in the table. However, changes that appear only in the full Protocol are described in the table. A redlined version of the protocol shows all revisions in tracked changes.

**Table 1: Detailed Summary of Changes**

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| **Cover Page** | Version 1.0, Original date: 1st March 2023<br>Version 1.1 date: 2nd March 2023<br>Version 2.0 date: 5th April 2023<br>Version 3.0 date: 12th October 2023 | Version 1.0, Original date: 1st March 2023<br>Version 1.1 date: 2nd March 2023<br>Version 2.0 date: 5th April 2023<br>Version 3.0 date: 12th October 2023<br>**Version 3.1 date: 30th October 2023** | Administrative update. |
| **Signature Page** | 1.0/01 March 2023<br>1.1/02 March 2023<br>2.0/05 April 2023<br>3.0/12 October 2023 | 1.0/01 March 2023<br>1.1/02 March 2023<br>2.0/05 April 2023<br>3.0/12 October 2023<br>**3.1/30 October 2023** | Administrative update. |
| **Section 1.4.2** | …<br>The IVT route was used in the ocular toxicology studies in rabbits and dogs. In the GLP repeat dose dog ocular toxicology study, dogs were dosed up to 3.81 mg/eye, which is an approximate human equivalent dose of 8.31 mg/eye scaled by vitreous volume (2.2mL in dog vs 4.8mL in human). The maximum intended dose of EYE103 in the clinic is 800 µg/eye. The completed 9-week GLP ocular toxicology study in dogs mimicked the clinical dose regimen in this | **…**<br>The IVT route was used in the ocular toxicology studies in rabbits and dogs. In the GLP repeat dose dog ocular toxicology study, dogs were dosed up to 3.81 mg/eye, which is an approximate human equivalent dose of 8.31 mg/eye scaled by vitreous volume (2.2mL in dog vs 4.8mL in human). The maximum intended dose of EYE103 in the clinic is 800 µg/eye. The completed 9-week GLP ocular toxicology study in dogs mimicked the clinical dose regimen in this study, with | Data from Part 1 of the study shows a good safety profile in the participants treated to date and supports the safety of treating participants for longer |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | study, with once monthly dosing on Days 1, 29, and 57. | once monthly dosing on Days 1, 29, and 57. **This study (EYE103-101) has been ongoing for 6 months and there have been no issues to date that prevents extending dosing in humans.** | |
| **Synopsis and Section 3.1.1. and 3.2 In multiple places wherever Week 12 follow-up visit is referred to** | …<br>Week 12<br>… | …<br>Week 12 **(or Week 24 for the extended treatment participants)**.<br>… | Administrative |
| **Synopsis and Section 3.1.2.** | Additional new sentence | **…**<br>**In addition, participants in both Part 1 and Part 2 at up to 5 selected sites, may elect to receive 3 additional injections at Weeks 12, 16, 20 with a follow-up visit at Week 24.** | Data from Part 1 of the study shows a good safety profile in the participants treated to date and supports the safety of treating participants for longer |
| **Synopsis and Section 3.2. Study Procedures** | …<br>In both the MAD and dose-finding parts of the study, samples for ADA analyses will be collected prior to dosing on treatment days on Day 1, Weeks 4 and 8, and again at Week 12. In the dose-finding part of the | **…**<br>In both the MAD and dose-finding parts of the study, samples for ADA analyses will be collected prior to dosing on treatment days on Day 1, Weeks 4 and 8, and again at Week 12. In the dose-finding part of the | Data from Part 1 of the study shows a good safety profile in the participants treated to date and supports the safety |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | study, samples for PK analyses will be collected at the same time points as those for the ADA samples. The exact time and date of sample collection must be recorded according to the instructions in the Laboratory Manual, which will also provide details on the collection method and volumes for all PK and ADA samples. | study, samples for PK analyses will be collected at the same time points as those for the ADA samples. The exact time and date of sample collection must be recorded according to the instructions in the Laboratory Manual, which will also provide details on the collection method and volumes for all PK and ADA samples. **Participants who elect to receive 3 additional study treatments at Weeks 12, 16 and 20 will undergo the study asssessments outlined in Section 6.3 and will undergo the same follow-up assessments at the Week 24 visit as they would otherwise have had at the Week 12 visit.** | of treating participants for longer |
| | In addition, the following will be recorded for all participants at approximately 12 weeks after each participant's last dose of EYE103: a retrospective patient chart review of all AEs and Con Meds, VA, and any CST measurements from the time between their Week 12 visit and the 24-week timepoint. | In addition, the following will be recorded for all participants at approximately 12 weeks after each participant's ~~last dose of EYE103~~ **4-week follow-up visit**: a retrospective patient chart review of all AEs and Con Meds, VA, and any CST measurements from the time between their Week 12 visit and the 24-week timepoint **(for partcipants who receive a total of 3 study treatments). A retrospective chart review of the same parameters will also be made for the participants who agree to 3 additional treatments for the period** | |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | | **between their Week 24 follow-up visit and Week 36.** | |
| **Synopsis and Section 4.1** | The study plans to enroll approximately 92 participants (12 in the MAD part and 80 in the dose-finding part). | The study plans to enroll approximately 92 participants (**Approximately**12 in the MAD part and **approximately** 80 in the dose-finding part). | Administrative change |
| **Synopsis and new Section 4.3.3.** | New Section | **4.3.3. DME-Specific Inclusion Criteria for Extended Treatment**<br>**1. Any DME participant with a significantly positive anatomic response at their 4-week follow-up visit i.e. >90% resolution of excess retinal fluid on SDOCT and with prior approval of the sponsor** | |
| **Synopsis and new Section 4.3.5.** | New Section | **4.3.5. NVAMD-Specific Inclusion Criteria for Extended Treatment**<br>**1. Any NVAMD participant receiving combination therapy with anti-VEGF and with prior approval of the sponsor** | |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| **Section 6.1.1.** | All participants will receive a written informed consent form (ICF) describing this study and be provided with sufficient information to make an informed decision about participating in this study. Additional consent will be required for the subset of participants who agree to participate in the sub study with iCare HOME2 tonometers. | All participants will receive a written informed consent form (ICF) describing this study and be provided with sufficient information to make an informed decision about participating in this study. Additional consent will be required for the subset of participants who agree to participate in the sub study with iCare HOME2 tonometers. **Furthermore, an additional written informed consent will be required for participants who elect to receive 3 additional study treatments starting at Week 12.** | Administrative requirement |
| **Section 6.3** | New Section Added | **6.3 Conduct of Study for Participants electing to have 3 additional treatments**<br>**6.3.1. Visit 6 – Week 12 (±3 days)**<br>**The following procedures will be performed before study injections:**<br>• **Additonal informed consent for extended treatment**<br>• **Elibility sponsor approval**<br>• **Vital signs**<br>• **Fundoscopy and biomicroscopy** | Data from Part 1 of the study shows a good safety profile in the participants treated to date and supports the safety of treating participants for longer |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | | • **IOP**<br>• **ETDRS BCVA**<br>• **SDOCT**<br>• **OCTA (if available)**<br>• **Urine pregnancy test (females of childbearing potential only)**<br>• **Blood samples for PK (within 30 minutes pre-injection)**<br>• **Blood samples for ADA (pre-dose)**<br>• **EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)**<br>• **Concomitant medications**<br>• **AEs**<br>**6.3.2. Telephone Call – 1 day post Week 12**<br>**The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.**<br>• **Concomitant medications** | |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | | • **AEs**<br>**6.3.3. Visit 7 – Week 16 (±3 days)**<br>**The following procedures will be performed before study injections:**<br>• **Vital signs**<br>• **Fundoscopy and biomicroscopy**<br>• **IOP**<br>• **ETDRS BCVA**<br>• **SDOCT**<br>• **OCTA (if available)**<br>• **Urine pregnancy test (females of childbearing potential only)**<br>• **Blood samples for ADA (pre-dose)**<br>• **EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)**<br>• **Concomitant medications**<br>• **AEs** | |

| | | | |
|---|---|---|---|
| | | **6.3.4. Telephone Call – 1 day post Week 16**<br>**The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.**<br>• **Concomitant medications**<br>• **AEs**<br>**6.3.5. Visit 8 – Week 20 (±3 days)**<br>**The following procedures will be performed before study injections:**<br>• **Vital signs**<br>• **Fundoscopy and biomicroscopy**<br>• **IOP**<br>• **ETDRS BCVA**<br>• **SDOCT**<br>• **OCTA (if available)**<br>• **Urine pregnancy test (females of childbearing potential only)**<br>• **Blood samples for ADA (pre-dose)**<br>• **EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)** | |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | | • **Concomitant medications**<br>• **AEs**<br>**6.3.6. Telephone Call – 1 day post Week 20**<br>**The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.**<br>• **Concomitant medications**<br>• **AEs**<br>**6.3.7. Visit 9 - Week 24 (±3 days) - Follow-Up or Early Termination Visit**<br>**The following procedures will be performed:**<br>• **Complete physical examination**<br>• **Vital signs**<br>• **Fundoscopy and biomicroscopy**<br>• **IOP**<br>• **ETDRS BCVA**<br>• **FA**<br>• **CFP** | |

| Protocol Section/ Location | Protocol Version 3.0, Amendment Date 12Oct2023 | Protocol Version 3.1, Amendment Date 30Oct2023 | Reason for Change |
|---|---|---|---|
| | | • **SDOCT**<br>• **OCTA (if available)**<br>• **Fasting laboratory assessments (serum chemistry and lipid panel, hematology, coagulation panel)**<br>• **Urine pregnancy test (females of childbearing potential only)**<br>• **Blood samples for ADA**<br>• **Concomitant medications**<br>• **AEs** | |

The following addtional Schedule of Assessments added:

## Schedule of Assessments for Patients who Elect to receive 3 additional treatments

| Visit # | V6 | *T4* | V7 | *T5* | V8 | *T6* | V9 |
|---|---|---|---|---|---|---|---|
| **Study Week** | **W12 ±3 days** | **1 day post W12** | **W16 ±3 days** | **1 day post W16** | **W20 ±3 days** | **1 day post W20** | **W24 ±3 days** |
| **Informed Consent** | X | | | | | | |
| **Eligibility and Approval** | X | | | | | | |
| **Vital signs** | X | | X | | X | | X |
| **Fundoscopy/biomicroscopy** | X | | X | | X | | X |
| **IOP[d]** | X | | X | | X | | X |
| **ETDRS BCVA** | X | | X | | X | | X |
| **FA** | | | | | | | X |
| **CFP** | | | | | | | X |
| **SDOCT** | X | | X | | X | | X |
| **OCTA if available** | X | | X | | X | | X |
| **Laboratory assessments[a]** | | | | | | | X[a] |
| **Pregnancy test[b]** | X[b] | | X[b] | | X[b] | | X[b] |
| **Blood samples for PK[c]** | X | | | | | | |
| **Blood samples for ADA** | X | | X | | X | | X |
| **IVT of EYE103 & anti-VEGF[d]** | X | | X | | X | | |
| **Concomitant medications** | X[b] | X | X[b] | X | X[b] | X | X |
| **AEs** | X[c] | X | X[c] | X | X[c] | X | X |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BCVA = best-corrected visual acuity; CFP = color fundus photos; ETDRS = early treatment of diabetic retinopathy study; FA = fluorescein angiography; IOP = intraocular pressure; IVT = intravitreal injection; OCTA = optical coherence tomography angiography; PK = pharmacokinetics; SDOCT = spectral domain optical coherence tomography; T= telephone call to participant; V = participant visit to study site

[a] Laboratory assessments (HbA1c is only at screening) for safety must be collected after an overnight fast

[b] Pregnancy test will be serum at the Screening Visit and urine on all subsequent days (for females of childbearing potential). If urine sample is positive this should be confirmed by a serum test.
[c] The blood samples on the IVT days for PK will be drawn within 30 minutes before the IVT.
[d] There must be at least 30 minute separation and normalisation of IOP between EYE103 and the second anti-VEGF injection in NVAMD participants.
[e] Follow-Up or Early Termination visit



# EYE103-101

A 2-part study consisting of an open-label multiple ascending dose (MAD) safety study, and a dose-finding single-masked comparative safety and preliminary efficacy study of intravitreal (IVT) EYE103 in a mixed population of participants with diabetic macular edema (DME) and neovascular age-related macular degeneration (NVAMD)

Version 1.0, Original date: 1st March 2023
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Version 2.0 date: 5th April 2023
Version 3.0 date: 11th October 2023
Version 3.1 date: 30th October 2023

IND #: 163412
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The information in this document is confidential and will not be disclosed to others without written authorization from Eyebiotech Ltd., except to the extent necessary to obtain informed consent from persons involved in the clinical study or their legal guardians, or for discussions with local regulatory authorities, ethics committees (EC), Institutional Review Boards (IRB), or persons participating in the conduct of the study

## INVESTIGATOR'S AGREEMENT

### Study Title

A 2-part study consisting of an open-label multiple ascending dose (MAD) safety study, and a dose-finding single-masked comparative safety and preliminary efficacy study of intravitreal (IVT) EYE103 in a mixed population of participants with diabetic macular edema (DME) and neovascular age-related macular degeneration (NVAMD)

My signature confirms that I have carefully read, and that I understand this protocol. I agree to follow the study procedures as outlined in this protocol in compliance with Good Clinical Practice and all other regulatory requirements, including provision for the well-being of the study participants according to the ethical principles stated in the Declaration of Helsinki.

This protocol and the referenced Investigator's Brochure contain confidential information with respect to products and clinical studies. I agree to hold this information in confidence and not to disclose it to any third parties until this information becomes a matter of public knowledge, or until a formal agreement for that purpose has been entered into by the parties.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

# SIGNATURE PAGE

Title: A 2-part study consisting of an open-label multiple ascending dose (MAD) safety study, and a dose-finding single-masked comparative safety and preliminary efficacy study of intravitreal (IVT) EYE103 in a mixed population of participants with diabetic macular edema (DME) and neovascular age-related macular degeneration (NVAMD)

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3.1/30 October 2023

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Table of Contents

LIST OF FIGURES ..... 7
SYNOPSIS ..... 8
NVAMD-Specific Inclusion Criteria for Extended Treatment ..... 14
LIST OF ABBREVIATIONS ..... 18
1. INTRODUCTION ..... 22
1.1. Diabetic Macular Edema ..... 22
1.2. Neovascular Age-Related Macular Degeneration ..... 24
1.3. CCI ..... 25
1.4. CCI ..... 25
1.4.1. CCI ..... 25
1.4.2. CCI ..... 26
1.5. CCI ..... 27
2. STUDY OBJECTIVES AND ENDPOINTS ..... 27
2.1. Objective ..... 27
2.2. Safety Endpoints ..... 27
2.3. Efficacy Endpoints ..... 28
2.3.1. Primary Efficacy Endpoint ..... 28
2.3.2. Other Efficacy Endpoints ..... 28
2.4. PK Endpoints ..... 28
2.5. Other Endpoints ..... 28
3. INVESTIGATIONAL PLAN ..... 28
3.1. Overall Study Design ..... 28
3.1.1. Part 1: Multiple Ascending Dose ..... 28
3.1.2. Part 2: Dose-finding Efficacy ..... 30
3.2. Study Procedures ..... 31
4. SELECTION AND WITHDRAWAL OF PARTICIPANTS ..... 33
4.1. Number of participants ..... 33
4.2. Number and Location of Study Sites ..... 33
4.3. Participant Eligibility Criteria ..... 33
4.3.1. General Inclusion Criteria ..... 33
4.3.2. DME-Specific Inclusion Criteria ..... 33
4.3.3. DME-Specific Inclusion Criteria for Extended Treatment ..... 34
4.3.4. NVAMD-Specific Inclusion Criteria ..... 34
4.3.5. NVAMD-Specific Inclusion Criteria for Extended Treatment ..... 34
4.3.6. General Exclusion Criteria ..... 34
4.3.7. DME-Specific Exclusion Criteria ..... 35
4.3.8. NVAMD-Specific Exclusion Criteria ..... 36

4.4. Withdrawal of Participants ..... 36
4.5. Rescue Treatment For Participants ..... 37
4.6. Follow-up of Participants with AEs ..... 37
5. TREATMENT OF PARTICIPANTS ..... 37
5.1. Description of EYE103 ..... 37
5.1.1. Storage, Accountability and Compliance ..... 38
5.2. Prior and Concomitant Medications ..... 38
5.2.1. Prohibited Concomitant Medications ..... 38
6. CONDUCT OF STUDY AND STUDY VISITS ..... 38
6.1. Conduct of Study: Part 1 MAD Cohorts ..... 38
6.1.1. Screening and Informed Consent ..... 38
6.1.2. Visit 1 – Screening (Day -28 to Day -1) ..... 39
6.1.3. Visit 2 – Day 1 (1st IVT) ..... 39
6.1.4. Telephone Call – Day 2 ..... 40
6.1.5. Visit 3 – Day 4 ..... 40
6.1.6. Visit 4 – Day 8 (±3 days) ..... 40
6.1.7. Visit 5 – Week 4 – Day 29 (±3 days) (2nd IVT) ..... 41
6.1.8. Telephone Call – 1 day post Week 4 ..... 41
6.1.9. Visit 6 – Week 8 - Day 57 (±3 days) (3rd IVT) ..... 41
6.1.10. Telephone Call – 1 day post Week 8 (Day 58) ..... 42
6.1.11. Visit 7 – Day 60 ..... 42
6.1.12. Visit 8 – Week 9 – Day 64 (±3 days) ..... 42
6.1.13. Visit 9 – Week 12 – Day 85 (±3 days) Follow-Up or Early Termination Visit ..... 42
6.2. Conduct of Study: Part 2 Dose-Finding Cohorts ..... 43
6.2.1. Screening and Informed Consent ..... 43
6.2.2. Visit 1 - Screening (Day -28 to Day -1) ..... 43
6.2.3. Visit 2 – Day 1 (1st IVT) ..... 44
6.2.4. Telephone Call – Day 2 ..... 44
6.2.5. Study Visit for Subjects in the iCare HOME2 Sub Study ..... 44
6.2.6. Visit 3 – Day 8 (±2 days) ..... 45
6.2.7. Visit 4 – Week 4 (±3 days) (2nd IVT) ..... 45
6.2.8. Telephone Call – 1 day post Week 4 ..... 45
6.2.9. Visit 5 – Week 8 (±3 days) (3rd IVT) ..... 45
6.2.10. Telephone Call – 1 day post Week 8 ..... 46
6.2.11. Visit 6 – Week 12 (±3 days) Follow-Up or Early Termination Visit ..... 46
6.3. Conduct of Study for Participants electing to have 3 additional treatments ..... 47
6.3.1. Visit 6 – Week 12 (±3 days) ..... 47
6.3.2. Telephone Call – 1 day post Week 12 ..... 47

6.3.3. Visit 7 – Week 16 (±3 days) ..... 47
6.3.4. Telephone Call – 1 day post Week 16 ..... 48
6.3.5. Visit 8 – Week 20 (±3 days) ..... 48
6.3.6. Telephone Call – 1 day post Week 20 ..... 48
6.3.7. Visit 9 - Week 24 (±3 days) - Follow-Up or Early Termination Visit ..... 48
7. OPHTHALMOLOGY ASSESSMENTS ..... 49
7.1. Intraocular Pressure ..... 49
7.2. Biomicroscopy ..... 49
7.3. Fundoscopy ..... 49
7.4. Best Corrected Visual Acuity ..... 49
7.5. Colour Fundus Photography ..... 50
7.6. Fluorescein Angiography ..... 50
7.7. Spectral Domain Optical Coherence Tomography ..... 50
7.8. Optical Coherence Tomography Angiography ..... 50
8. SAFETY ASSESSMENTS FOR ALL PARTICIPANTS ..... 50
8.1. Medical History ..... 50
8.2. Vital Signs ..... 50
8.3. Physical Examination ..... 51
8.4. Electrocardiogram ..... 51
8.5. Laboratory Assessments ..... 51
9. SAFETY MONITORING ..... 51
9.1. Data Safety Monitoring Board ..... 52
9.2. Definitions of AEs ..... 52
9.3. Serious Adverse Events ..... 53
9.4. Adverse Event Recording and Reporting ..... 54
9.5. Classification of Adverse Events ..... 54
9.5.1. Intensity/Severity ..... 54
9.5.2. Expectedness ..... 54
9.5.3. Relatedness ..... 55
9.5.4. Outcome ..... 55
9.5.5. Action Taken with Study Drug ..... 55
9.6. Serious Adverse Event Reporting ..... 55
10. STATISTICS ..... 56
10.1. Statistical Methodology ..... 56
10.1.1. Randomization ..... 56
10.1.2. Description of Populations for Analysis ..... 56
10.2. Sample Size ..... 57
10.3. Endpoints ..... 57

10.3.1. Safety Endpoints ..... 57
10.3.2. Pharmacokinetic Endpoints ..... 57
10.4. Analysis of Safety ..... 57
10.5. Analysis of PK Endpoints ..... 58
10.6. Analysis of Efficacy Endpoints ..... 58
11. DATA HANDLING AND RECORDKEEPING ..... 58
11.1. Data Collection ..... 58
11.2. Study Monitoring ..... 59
11.3. Study Documentation and Retention of Records ..... 59
11.4. Audits and Inspections ..... 60
11.5. Quality Control and Quality Assurance ..... 60
11.6. Amendments to the Protocol ..... 60
12. ETHICS ..... 60
12.1. IRB/EC Review ..... 60
12.2. Ethical Conduct of the Study ..... 61
12.3. Participant Confidentiality ..... 61
12.4. Disclosure and Publication Policy ..... 62
13. REFERENCES ..... 63
APPENDIX A : SCHEDULE OF ASSESSMENTS ..... 66
Schedule of Assessments for Part 1: MAD ..... 66
Schedule of Assessments for Part 2: Dose-finding ..... 68
Schedule of Assessments for Patients who Elect to receive 3 additional treatments ..... 69
APPENDIX B : DRUG ADMINISTRATION AND INJECTON PROCEDURE ..... 71
APPENDIX C : SPONSOR'S COMMITMENTS ..... 73
APPENDIX D : COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS ..... 74
APPENDIX E : DEFINITION OF OCULAR DOSE-LIMITING TOXICITIES (DLTS) ..... 75
(a) Ophthalmic DLT ..... 75
*(i)* Clinical Examination ..... 75
*(ii)* Fluorescein Angiogram ..... 75
(b) Systemic DLT ..... 75
APPENDIX F : CONTRACEPTION GUIDELINES ..... 76

## LIST OF FIGURES

Figure 1: Part 1: MAD Study Schematic ..... 29
Figure 2: Part 2: Dose-Finding Study Schematic ..... 31

# SYNOPSIS

| | |
|---|---|
| | **Name of Sponsor/Company:** Eyebiotech Ltd. |
| | **Protocol Number:** EYE103-101 |
| | **Title of Study:** A 2-part study consisting of an open-label multiple ascending dose (MAD) safety study, and a dose-finding single-masked comparative safety and preliminary efficacy study of intravitreal (IVT) EYE103 in a mixed population of participants with diabetic macular edema (DME) and neovascular age-related macular degeneration (NVAMD)<br>***Short Title:*** *A phase 1b/2a safety and preliminary efficacy study of EYE103 in DME and NVAMD participants* |
| | **Phase of Study:** 1b/2a |
| | **Number of Participants (planned):** Approximately 92 participants (approximately12 in the MAD part and approximately 80 in the dose-finding part) |
| | **Number of Study Sites:** Approximately 50 sites in Argentina, Israel, the United Kingdom (UK), and the United States (US) |
| | **Objectives:** The objectives of the study are to evaluate the safety, tolerability, preliminary efficacy, and pharmacokinetic (PK) profile of intravitreal injection (IVT) EYE103 |
| | **Safety Endpoints**<br>• Adverse events (AEs), serious adverse events (SAEs), and laboratory assessments will be monitored and recorded throughout the duration of the study<br>**Primary Efficacy Endpoint**<br>• Mean change in best-corrected visual acuity (BCVA) using the standardized ETDRS (Early Treatment of Diabetic Retinopathy Study) chart from baseline to Week 12 in the study eye of the participants diagnosed with DME or NVAMD<br>**Other Efficacy Endpoints**<br>• Early treatment of diabetic retinopathy study BCVA response, defined as a gain from baseline in the study eye by 15 or more letters (DME and NVAMD participants) at Week 12<br>• Mean change in retinal central subfield thickness (CST) from baseline in the study eye based on spectral domain optical coherence tomography (SDOCT) (DME and NVAMD participants) at Week 12<br>• Percentage of patients with loss of vision from baseline in the study eye by 15 or more letters (DME and NVAMD participants) at Week 12<br>**Other Endpoints**<br>• Pharmacokinetic (PK) assessment and anti-drug antibody (ADA) levels will be analysed |

**Trial Design:**

This study will be in 2 parts: an open-label, uncontrolled MAD portion of the study followed by a randomized, single-masked, comparative, dose-finding portion of the study in which both the participants and site personnel, including the physician assessing safety and efficacy, are masked to the dose-level.

**Part 1 - MAD**

In this portion of the study, which will only be conducted in the USA, 4 cohorts, each comprised of 3 participants, will receive IVT EYE103 at 4 dose levels in ascending order CCI in an open-label and uncontrolled design. The participants will be comprised of a mixed population who will be comprised of: (1) naïve participants with DME who will receive EYE103 as monotherapy, (2) participants naïve to anti-VEGF with NVAMD, or (3) anti-VEGF experienced participants with NVAMD. Participants with NVAMD will receive EYE103 in combination with aflibercept, if naïve, or their previously utilized anti-VEGF agent, if experienced (2 mg aflibercept, 0.5 mg ranibizumab, or 1.25 mg bevacizumab), given 30 minutes apart by IVT. There will be no restriction on the proportion of participants enrolled from each of the 3 populations.

The first 3 participants will be enrolled into Cohort 1, and, on Day 1, will receive an IVT injection of 0.05 mg of EYE103 (± anti-VEGF) in the eye selected as the study eye (i.e., the eye with the worst vision). The study site will call each participant the following day (24 ±4 hours) to confirm whether there have been any adverse signs or symptoms. Participants will return 1 week later (Day 8 ±1 day after the first dose) to be examined for any adverse changes. Participants will also be instructed to call the study site at any time between study visits to discuss any concerns about their treatment. Participants will return at Week 4 (i.e., 4 weeks after the first injection) to receive their second dose. The study site will again call each participant the following day (24 ±4 hours) to confirm that there have been no adverse signs or symptoms, and the participants will be instructed to call the site if there any concerns about their treatment. The participants will then return at Week 8 for their final injection and again will receive a telephone call from the study site the following day (24 ±4 hours). All participants will return for their final study assessments at Week 12 (or Week 24 for the extended treatment participants).

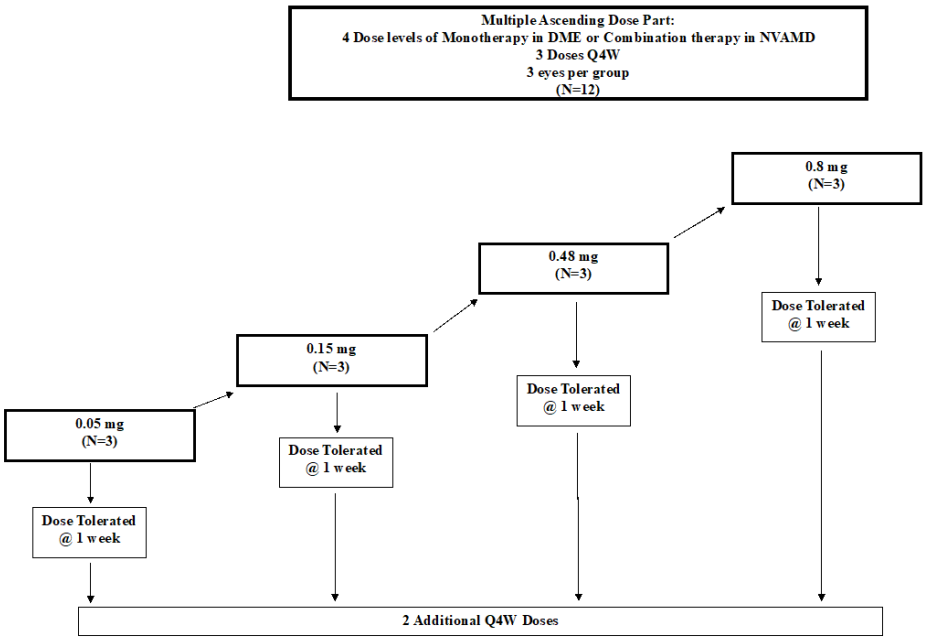
Participants in Cohort 2 will receive their first IVT injection of 0.15 mg of EYE103 once all 3 participants in Cohort 1 have received their first doses of EYE103 and have completed their Day 8 visits confirming safety. Cohort 2 participants will then receive their second and third injections following the identical protocol to Cohort 1 and will be required to attend their follow-up visit at Week 12 (or Week 24 for the extended treatment participants).

Similarly, participants in Cohorts 3 and 4 (the 0.48 mg and 0.8 mg doses respectively) will follow the identical protocols as Cohorts 1 and 2 and commence dosing when all 3 participants in the preceding cohort have received their first dose and completed their Day 8 safety visits. Again, participants will receive their second and third doses of EYE103 at Weeks 4 and 8 and complete their follow-up visits at Week 12 (or Week 24 for the extended treatment participants) following the same protocol procedures as Cohorts 1 and 2.

If at any time a participant experiences a dose-limiting toxicity (DLT) (defined as an AE with a severity ≥ Grade 3 on the Common Terminology Criteria for Adverse Events (CTCAE) scale for systemic DLTs in Appendix D, or as defined in Appendix E for ocular DLTs), then the data safety monitoring board (DSMB) will be informed and the cohort at

which the DLT occurred will be expanded to include 3 more participants (to a total of 6 participants). Any enrollment of participants at a higher dose level than that at which the DLT occurred will be put on hold until resumption of enrollment is agreed and the DSMB informed. If a second DLT occurs at the same dose level, then all treatments at that dose level and higher will be halted, and the dose below that dose level will be considered as the maximum tolerated dose (MTD). The sponsor may also choose to add an additional 3 participants to any dose cohort to further assess the drug profile. In addition, participants in both Part 1 and Part 2, at up to 5 selected sites, may elect to receive 3 additional injections at Weeks 12, 16, and 20 with a follow-up visit at Week 24.

**Figure 1: Part 1 - MAD Study Schematic**



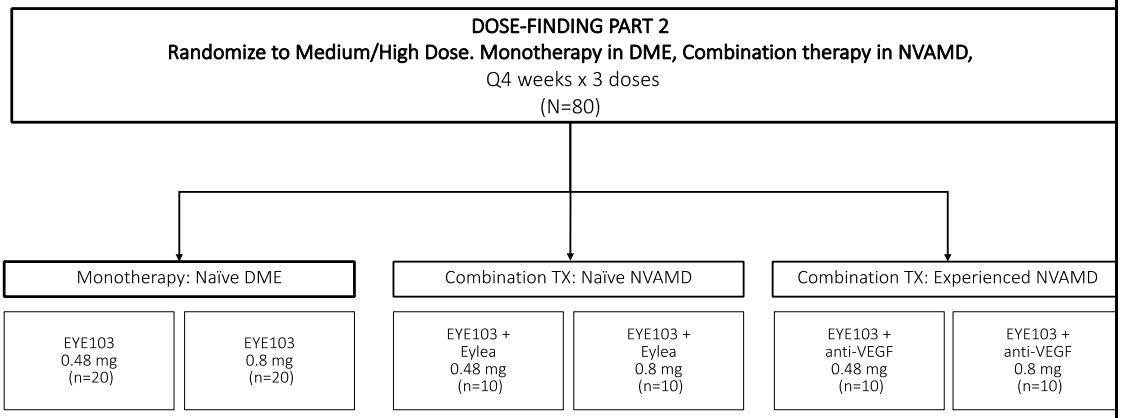

Note: If at any time a participant in any of the dose group cohorts experiences a DLT, defined as a related AE with a severity ≥ Grade 3 on the CTCAE scale, then the DSMB will be informed and the cohort at which the DLT occurred will be expanded to include 3 more participants (to a total of 6 participants). Any enrollment of participants at a higher dose level than that at which the DLT occurred will be put on hold until resumption of enrollment is agreed and the DSMB is informed. If a second DLT occurs at the same dose level, then all treatments at that dose level and higher will be halted, and the dose below that dose level will be considered as the MTD.

### Part 2 – Dose-Finding

Once the last participant in the MAD portion of the study has received their first dose, completed their Day 8 safety visit and the MTD either has been determined or declared as not having been reached at the doses tested, two of the four doses will be selected for inclusion in this dose-finding study, based on safety and any preliminary efficacy signals observed.

This dose-finding part of the study will be randomized and masked to both the participants and study site personnel, except to the unmasked site personnel preparing the syringes for injection. The dose-finding part of the study will be divided according to whether the participants are naïve DME participants, naïve NVAMD participants, or experienced NVAMD participants: 2 cohorts each consisting of 20 naïve DME participants will be randomized (1:1) to one of two doses of EYE103, which they will receive as monotherapy; 2 cohorts, each consisting of 10 naïve NVAMD participants, will be randomized (1:1) to one of the 2 selected doses of EYE103, which will be given in combination with 2 mg aflibercept 30 minutes apart; and 2 cohorts, each consisting of 10 experienced NVAMD participants, will be randomized (1:1) to one of the two doses of EYE103, which will be given in combination with their previously utilized anti-VEGF agent (2 mg aflibercept, 0.5 mg ranibizumab, or 1.25 mg bevacizumab), given 30 minutes apart by IVT. Enrollment may be directed into specific disease cohorts at the sponsor's discretion. Allocation into the groups will always be performed using 1:1 randomization within each disease cohort. In addition, participants in both Part 1 and Part 2 at up to 5 selected sites, may elect to receive 3 additional injections at Weeks 12, 16, 20 with a follow-up visit at Week 24.

**Figure 2: Part 2 - Dose-Finding Study Schematic**




**Study Procedures: Part 1 MAD and Part 2 Dose-Finding**

All participants will be screened within 28 days prior to treatment and will have physical examinations and vital signs collected to exclude any abnormalities that would preclude their participation in the study. A physical examination will be repeated at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit, and vital signs, together with AEs and concomitant medications, will be performed/recorded at all study visits.

For the MAD part of the study only, electrocardiograms (ECGs) will be performed at Screening and 3 days (±1 day) after the first and third injections, and again at the Week 12

(or Week 24 for the extended treatment participants) follow-up visit. Once an initial diagnosis of DME or NVAMD is determined, participants will undergo the following assessments to confirm eligibility: full medical and ocular history, ETDRS BCVA, biomicroscopy, fundoscopy, intraocular pressure (IOP) measurement, spectral domain optical coherence tomography (SDOCT), fluorescein angiography (FA), and color fundus photography (CFP), and these will be repeated at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. In addition, for sites with optical coherence tomography angiography (OCTA) capability, OCTA will be performed at the same timepoints that SDOCT is performed.

All ophthalmology assessments will be performed on both eyes throughout the study. Eligibility based on FA, CFP, and SDOCT (OCTA, if available) will be determined by the independent reading center (IRC). Participants will also receive a telephone call from study site personnel (24 ±4 hours) after each injection to confirm that no untoward effects have occurred following the IVT. However, participants may choose to return to the study site the following day for an eye exam and IOP measurement if that is their preference.

For the MAD part of the study only, all participants will return to the study site for biomicroscopy, fundoscopy, SDOCT (OCTA, if available), and IOP measurements 1 week after the first injection (Day 8) in each of the 4 dose cohorts.

In the dose-finding part of the study only, there will be a small sub study conducted in a subgroup of US participants: 20 participants will be consented separately for the sub study, and those that agree will each be provided with iCare HOME2 tonometers, with which they will be instructed (after training) to record the IOPs of both eyes twice a day 12 hours (±1 hour) apart (preferably 8:00 am and 8:00 pm) for 1 week following each injection. In addition, participants in the sub study will return to the study site (24 ±4 hours) after the first injection for IOP measurement.

In both the MAD and dose-finding parts of the study, BCVA, biomicroscopy, fundoscopy, IOP, SDOCT, and OCTA will be repeated prior to each treatment at the Week 4 and 8 visits, and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. In addition, FA and CFP will be repeated at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. Concomitant medications and AEs will be recorded at all visits and elicited during the safety follow-up telephone calls. Clinical laboratory tests will include overnight fasting serum chemistry, lipid panel, hematology, HbA1c (Screening only) and coagulation profile. All women of childbearing potential will have a serum pregnancy test at Screening and urine pregnancy test prior to each dose and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. The clinical laboratory tests will be performed at Screening and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. An additional visit one week after the first dose (Day 8 ±2 days) in the dose-finding study will assess BCVA, SDOCT (and OCTA if available), IOP, AEs and concomitant medications.

In the MAD part of the study only, comprehensive blood sampling for PK analyses will be collected at the following time points: within 30 minutes before and 4 hours (±1 hour) following the first dose (Day 1), 3 days (±1 day) after the first dose (Day 4), Day 8 (±3 days), within 30 minutes prior to the second dose at Week 4 (±3 days), within 30 minutes prior to, and 4 hours (±1 hour) after the third dose (Week 8), 3 days (±1 day)

| | |
|---|---|
| | and 8 days (±3 days) after the third dose, and finally again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit.<br><br>Samples for anti-drug antibody (ADA) analyses will be collected prior to dosing on treatment days on Day 1, and Weeks 4 and 8, and again at Week 12 (or Week 24 for the extended treatment participants) in both the MAD and dose-finding parts of the study. Samples for PK analyses will be collected at the same time points as those for the ADA samples in the dose-finding part of the study. The exact time and date of sample collection must be recorded according to the instructions in the Laboratory Manual, which will also provide details on the collection method and volumes for all ADA and PK samples. Participants who elect to receive 3 additional study treatments at Weeks 12, 16 and 20 will undergo the study assessments outlined in Section 6.3 and will undergo the same follow-up assessments at the Week 24 visit as they would otherwise have had at the Week 12 visit.<br><br>In addition, the following will be recorded for all participants at approximately 12 weeks after each participant's 4-week follow-up visit: a retrospective patient chart review of all AEs and Con Meds, VA, and any CST measurements from the time between their Week 12 visit and the 24-week timepoint (for participants who receive a total of 3 study treatments). A retrospective chart review of the same parameters will also be made for the participants who agree to 3 additional treatments for the period between their Week 24 follow-up visit and Week 36. |
| | **General Inclusion Criteria:**<br>Participants must:<br>1. Be willing and able to understand the study procedures and the risks involved and provide written informed consent before the first study-related activity<br>2. Be male or female ≥ 18 years of age<br>3. If female, have a negative serum pregnancy test at Screening and further negative urine tests immediately before each dose of study medication if the participant is a female of childbearing potential (including those with <2 years since the onset of menopause, amenorrhea for <1 year, or not surgically sterile); such participants must agree to use an acceptable method of contraception for 30 days after the last dose of study medication.<br>4. If male, be surgically sterile for at least 6 weeks, or agree to use an acceptable method of contraception, such as a condom and a second highly effective method of contraception from Screening up to and including 30 days after the last dose of study medication<br><br>**DME-Specific Inclusion Criteria:**<br>Participants must:<br>1. Have Type 1 or Type 2 diabetes mellitus and a HbA1c of ≤12%<br>2. Have a BCVA ETDRS letter score between 70 and 35 in the study eye<br>3. Have a decrease in vision in the study eye determined by the Investigator to be primarily the result of DME<br>4. Be treatment-naïve with vision loss in the study eye, and center involving DME diagnosed within 9 months of Screening |

5. Have a CST of ≥ 350 μm in the study eye on SDOCT as determined by the IRC at Screening

**DME-Specific Inclusion Criteria for Extended Treatment:**

1. Any DME participant with a significantly positive anatomic response at their 4-week follow-up visit i.e. >90% resolution of excess retinal fluid on SDOCT and with prior approval of the sponsor

**NVAMD-Specific Inclusion Criteria:**

Participants must:

1. Be ≥ 50 years of age
2. Have a BCVA ETDRS letter score between 70 and 35 in the study eye
3. Have either previously treated (experienced) or untreated (naïve) active subfoveal CNV or juxtafoveal CNV (with the lesion 1-199 μm from the fovea) with foveal involvement (demonstrated by leakage on FA and/or intraretinal (IR) fluid or subretinal fluid (SRF) on SDOCT) that is secondary to NVAMD where the total area of the lesion (including blood, neovascularization, and scar/atrophy) is ≤ 6 disc areas (DA), of which at least 50% must be active CNV
4. Foveal thickness ≥ 350 μm in the study eye on SDOCT as determined by the IRC at Screening
5. Be treatment-naïve with vision loss in the study eye secondary to NVAMD diagnosed within 2 weeks prior to the Day 1 study treatment (The **maximum** screening period for these participants is, therefore, 14 days)

   **OR**

   Have been diagnosed with NVAMD within the past 16 weeks and have received 3 anti-VEGF injections within the previous 14 weeks prior to Screening

**NVAMD-Specific Inclusion Criteria for Extended Treatment**

1. Any NVAMD participant receiving combination therapy with anti-VEGF and with prior approval of the sponsor

**General Exclusion Criteria**

Participants must not:

1. Be pregnant or breastfeeding
2. Have a history of cataract surgery and/or minimally invasive glaucoma surgery (MIGS) in the study eye within 3 months of Screening
3. Have had Yttrium-Aluminum Garnet (YAG) laser capsulotomy in the study eye within 2 months of Screening
4. Have had Pan-retinal Photocoagulation (PRP) or focal thermal laser photocoagulation in the study eye within 3 months of Screening
5. Have tractional retinal detachment in the study eye

6. Have uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye
7. Have had glaucoma-filtering surgery (trabeculectomy or tube shunt) in the study eye
8. Have any history of retinal detachment or treatment or surgery for retinal detachment in the study eye
9. Have had any use of regional depot steroids or intraocular steroids
10. Have any history of uveitis in either eye
11. Have significant media opacities, including cataract, in the study eye that might interfere with visual acuity, assessment of safety, OCT, or fundus photography
12. Have a cataract in the study eye that in the judgment of the Investigator is expected to require surgical extraction within 4 months of Screening
13. Have aphakia in the study eye
14. Have allergy to fluorescein dye
15. Have had vitrectomy in the study eye
16. Have known or former myopia with a spherical equivalent of >8 diopters
17. Have active retinal disease other than the condition under investigation in the study eye
18. Have any history or evidence of a concurrent ocular condition present in the study eye that, in the opinion of the Investigator, could require either medical or surgical intervention or affect macular edema or alter visual acuity during the study (e.g., vitreomacular traction, epiretinal membrane, other causes of CNV, such as pathological myopia, angiod streaks, presumed ocular histoplasmosis syndrome, and multifocal choroiditis)
19. Have active or suspected ocular or periocular infection or inflammation in either eye at Day 1
20. Currently have evidence of, or a history of any clinically significant autoimmune, cardiovascular, hematologic, hepatic, metabolic, peripheral vascular, renal, or respiratory disease, which, in the opinion of the Investigator, would exclude the participant from this study
21. Have a known hypersensitivity to any of the components of EYE103 formulation or prior hypersensitivity to monoclonal antibodies (mAbs)
22. Have previously participated in any study of EYE103 (participants in the MAD study may not subsequently enter the dose-finding study)
23. Presence of amblyopia, amaurosis or ocular disorders with BCVA <38 letters (ETDRS testing charts) in the fellow eye at screening

**DME-Specific Exclusion Criteria**

Participants must not:

1. Have macular edema in the study eye considered to be secondary to a cause other than DME (e.g., retinal vein occlusion [RVO], Irvine-Gass syndrome)
2. Have active iris or angle neovascularization or neovascular glaucoma in the study eye
3. Have proliferative diabetic retinopathy in the study eye, including any of the following features:
    a. Any vitreous or pre-retinal hemorrhage
    b. Neovascularization at optic disc
    c. Neovascularization elsewhere
4. Have structural damage to the center of the macula in the study eye that, in the opinion of the investigator or sponsor, is likely to preclude improvement in BCVA, including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, organized hard exudates in the foveal center, or other evidence of chronic disruption of the macular architecture

**NVAMD-Specific Exclusion Criteria**

Participants must not:

1. Have had previous thermal subfoveal laser therapy in the study eye
2. Have had previous photodynamic therapy (PDT) with Visudyne in the study eye
3. Have diabetic retinopathy in the study eye
4. Have the presence of significant and large serous pigment epithelial detachments (PEDs) **such as those** with a vertical height of ≥ 400 µm
5. Have the presence of a tear of the retinal pigment epithelium
6. Have a diagnosis of idiopathic polypoidal choroidal vasculopathy (IPCV)
7. Have fibrosis involving the foveal center or measuring more than 25% of the total lesion area and or juxtafoveal or sub-foveal geographic atrophy
8. Have structural damage to the center of the macula in the study eye that, in the opinion of the investigator or sponsor, is likely to preclude improvement in BCVA. This includes atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, organized hard exudates in the foveal center, or other evidence of chronic disruption the macular architecture

**Investigational Product, Dosage and Mode of Administration:**

CCI

[redacted]

**Statistical Methods:**

| | |
|---|---|
| | The MAD part of the study will be open-label and uncontrolled. The dose-finding part of the study will be single-masked to both participants and site personnel, except for the unmasked site personnel preparing the study medication syringes. Participants in the dose-finding part of the study will be randomized (1:1) to one of two dose levels selected from the MAD data for naïve DME participants, naïve NVAMD participants, or experienced NVAMD participants. For the naïve NVAMD participants, EYE103 will be given in combination with 2 mg aflibercept, and for the experienced NVAMD participants, EYE103 will be given in combination with their previously utilized anti-VEGF agent (2 mg aflibercept, 0.5 mg ranibizumab, or 1.25 mg bevacizumab), given 30 minutes apart by IVT.<br>Data from the participants in the MAD part of the study who received 1 of the 2 doses which were selected for the dose-finding study will be pooled with the data from the same dose levels in the dose-finding study. Descriptive statistics will be used. |

# LIST OF ABBREVIATIONS

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | adverse event |
| ADA | anti-drug antibody |
| AMD | age related macular degeneration |
| BCVA | best-corrected visual acuity |
| BRB | blood-retinal barrier |
| CFP | color fundus photography |
| CFR | code of federal regulations |
| CI | confidence interval |
| CL | clearance |
| $C_{max}$ | maximum serum concentration |
| CNS | central nervous system |
| CNV | choroidal neovascularization |
| CRO | contract research organization |
| CST | central subfield thickness |
| CTCAE | common terminology criteria for adverse events |
| DLT | dose-limiting toxicity |
| DSMB | data safety monitoring board |
| DME | diabetic macular edema |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| ETDRS | early treatment of diabetic retinopathy study |
| EU | european union |
| FA | fluorescein angiography |
| FDA | food and drug administration |
| FEVR | familial exudative vitreoretinopathy |
| FSH | follicle-stimulating hormone |
| FZD4 | frizzled-4 |
| GA | geographic atrophy |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| GCP | good clinical practice |
| GLM | general linear model |
| GLP | good laboratory practice |
| HbA1c | glycated hemoglobin A1c |
| HIPAA | health insurance portability and accountability act |
| IB | investigator's brochure |
| ICAM-1 | intracellular adhesion molecule 1 |
| ICF | informed consent form |
| ICH | international conference on harmonization |
| IDDI | international institute for drug development (the statistics and data management vendor for the study) |
| IgG | immunoglobulin G |
| IL-6 | interleukin-6 |
| IND | investigational new drug |
| IOP | intraocular pressure |
| IPCV | idiopathic polypoidal choroidal vasculopathy |
| IRB | institutional review board |
| IRC | independent reading center |
| ITT | intent-to-treat |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IVT | intravitreal injection |
| LEF | lymphoid enhancer factor |
| LM | laboratory manual |
| LRP5 | lipoprotein receptor-related protein 5 |
| MA | microaneurysm |
| mAb | monoclonal antibody |
| MAD | multiple ascending dose |
| MAR | missing at random |
| MIGS | minimally invasive glaucoma surgery |
| MTD | maximum tolerated dose |
| NCA | noncompartmental analyses |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| NDP | Norrie disease protein |
| NVAMD | neovascular age related macular degeneration |
| OCT | optical coherence tomography |
| OCTA | optical coherence tomography angiography |
| OD | oculus dextrus/dexter |
| OS | oculus sinister |
| PDGF-AA | platelet-derived growth factor AA |
| PDT | photodynamic therapy |
| PHI | protected health information |
| PK | pharmacokinetic |
| PPM | protocol procedures manual |
| PPV | pars plana vitrectomy |
| PRP | pan-retinal photocoagulation |
| Q4W | every 4 weeks |
| RPE | retinal pigment epithelium |
| RVO | retinal vein occlusion |
| Rx | therapy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDOCT | spectral domain optical coherence tomography |
| SOP | standard operating procedure |
| $t_{1/2}$ | terminal elimination half-life |
| TCF | T-cell factor |
| TEAE | treatment emergent adverse event |
| $T_{max}$ | time of maximum serum concentration |
| TSPAN12 | tetraspanin 12 |
| UK | united kingdom |
| US | united states |
| VEGF | vascular endothelial growth factor |
| $V_{ss}$ | volume of distribution at steady state |
| WHO | world health organization |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| YAG | yttrium-aluminum garnet |

# 1. INTRODUCTION

## 1.1. Diabetic Macular Edema

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetic retinopathy, with an increasing prevalence tied to the global epidemic of type 2 diabetes mellitus. The pathophysiology of DME starts with decreased retinal oxygen tension or retinal hypoxia that is likely the result of retinal capillary non-perfusion and/or drop out, which in turn leads to the upregulation of vascular endothelial growth factor (VEGF) that causes retinal capillary hyperpermeability. The foundation of treatment for type 2 diabetes is metabolic control of hyperglycemia and blood pressure, which is often insufficient to treat DME. Specific ophthalmic treatments for DME include intravitreal anti-VEGF drug(s) injections, intravitreal corticosteroid injections, focal laser photocoagulation, and vitrectomy, but a substantial fraction of eyes respond incompletely to these modalities, resulting in disordered retinal structure and vasculature and irreversible vision loss (Browning et al, 2018). The Wisconsin Epidemiologic Study of Diabetic Retinopathy found that 20% of patients with type 1 diabetes and 25% of patients with type 2 diabetes will develop DME after 10 years of follow-up, despite treatment for hyperglycemia and blood pressure control (Klein, 1984). In the United Kingdom (UK), it is estimated that 10% of the entire National Health Service budget is spent on the care of people with diabetes, 80% of which is spent on consequences and complications of diabetes, including DME (Al-Husainy et al, 2014), which represents a significant economic burden. Treatment goals for DME include reducing retinal thickness and neurosensory damage and minimizing the risk for potential adverse side effects to preserve vision (Shechtman, 2009).

Diabetic macular edema describes the accumulation of fluid in and under the central retina (the macula), which arises, in part, secondary to dysfunction of the blood-retinal barrier (BRB). Diabetic macular edema is caused by both extensive capillary leakage and focal leakage from grouped microaneurysms (MAs). Diabetic macular edema can occur in isolation without other signs of microangiopathy in the fundus; therefore, it merits being classified as a separate entity. Diabetic macular edema often results in blurred and distorted central vision, which is reflected in a reduction in measured best-corrected visual acuity (BCVA) (Schmidt-Erfurth, 2017).

There are a number of treatment options for patients with DME, but all have limited efficacy. As a result, there remains significant unmet need for patients, especially given the predicted increased economic burden associated with increasing diabetes rates.

Laser photocoagulation was the standard of care for the treatment of DME prior to the advent of the intravitreal injection approach. The efficacy of focal laser treatment has been related to the occlusion of leaking vessels, especially MAs, but the exact mechanism by which focal photocoagulation reduces DME is unknown. Laser photocoagulation is no longer considered standard of care, as improved efficacy can be obtained with pharmacotherapy (Schmidt-Erfurth, 2017). In addition, laser therapy is not effective in many cases of DME, particularly in cases of diffuse macular oedema. Patients also may experience complications following laser treatment, including scotoma and epiretinal membrane formation (Shechtman, 2009).

Diabetic macular edema stems from a complex pathogenesis, including the presence of a hypoxic environment in the microvasculature of patients with diabetic retinopathy. Hypoxia, in turn, leads to increased levels of VEGF, which is a potent vascular permeability factor and results in a state

of hyper-permeability of the retinal vessels. This complex cascade leads to vascular leakage and extracellular fluid accumulation, which eventually manifests as macular oedema. Vascular endothelial growth factor has been shown to play a critical role in the development of macular oedema, and high levels of VEGF have been found in the aqueous humor of patients with DME (Shechtman, 2009).

Intravitreal injections with anti-VEGF agents can reduce retinal oedema, improve vision, and prevent further visual loss in some patients (Kimoto and Kubota, 2012). These drugs have replaced laser photocoagulation as the standard of care because of their efficacy and safety profiles. Bevacizumab (Avastin®), ranibizumab (Lucentis®), and aflibercept (Eylea®) are all common treatments for DME with proven efficacy (over that of laser treatment) by improving visual acuity by 3 or more lines over the course of 1 year in 30-40% of patients (Virgili, 2018). Bevacizumab is a full-length, humanized, monoclonal antibody, ranibizumab is a recombinant humanized Fab fragment of a monoclonal antibody, and aflibercept is a recombinant decoy-receptor inhibitor of VEGF (Schmidt-Erfurth, 2017). Ranibizumab and aflibercept are approved for DME, whereas bevacizumab is an approved oncology treatment often used off-label in DME. Other anti-VEGF treatments include: brolucizumab (Beovu®), currently approved for DME and neovascular age related macular degeneration (NVAMD); faricimab (Vabysmo®), a bispecific antibody targeting both VEGF and angiopoietin-2 (Ang-2), approved in the UK, United States (US), and Japan for DME and NVAMD; and a biosimilar to ranibizumab, ranibizumab-nuna, currently approved for DME in the US.

Evidence highlights the role of inflammation in the development of DME. The pathological processes include retinal leukostasis, which is defined as the attachment of leukocytes inside the lumen of capillaries and is thought to be a major player and early event in the dysfunction of the BRB. Inflammation leads to the upregulation of intracellular adhesion molecule 1 (ICAM)-1, which mediates attraction of monocytes and neutrophils to the vascular endothelium to further enhance retinal leukostasis, vascular permeability, and breakdown of the BRB in diabetes (Schmidt-Erfurth, 2017).

Corticosteroids produce an anti-inflammatory effect through various mechanisms, including the decrease in the synthesis of inflammatory mediators, such as interleukin-6 (IL-6), interferon-inducible protein 10, monocyte-chemoattractant protein-1, as well as a decrease in platelet -derived growth factor AA (PDGF-AA) and VEGF synthesis. Intravitreal treatment with glucocorticoids has been found to significantly decrease the inflammatory processes by inhibition of ICAM-1 expression and leukostasis and improved overall BRB function. Triamcinolone acetonide, dexamethasone, and fluocinolone acetonide have all been used to treat DME (Schmidt-Erfurth, 2017). Long-acting intravitreal corticosteroids can achieve similar results in improving visual acuity to those of anti-VEGF therapies, with longer inter-injection intervals. Because of steroid-induced side effects (progression of cataract, glaucoma), these drugs are regarded as second-line medications (Barth, 2021). Surgery in the form of pars plana vitrectomy (PPV) also remains an option for patients with associated vitreoretinal traction, but the procedure remains controversial in non-tractional cases.

Due to limited efficacy and potential side effects of the currently approved treatments for DME, there remains a significant unmet need for a more efficacious and safer treatment. Since BRB breakdown and the resulting vascular hyper-permeability is a major disease driver in DME, it is a rational therapeutic target for DME, using EYE103, a Norrin mimetic, to restore BRB of the retinal

vessels by activating the FZD4/LRP5/ β-catenin pathway. EYE103 may result in restoration of the BRB competence and homeostasis and regression of DME and therefore represents a novel and potential therapeutic approach.

## 1.2. Neovascular Age-Related Macular Degeneration

Age related macular degeneration (AMD) has 2 main phenotypes, dry AMD and NVAMD. Dry AMD is more common and is associated with slow, non-neovascular damage to the retina. The most advanced form of dry AMD is called geographic atrophy (GA), which is characterised by degeneration of the retinal pigment epithelium (RPE), and severe, irreversible vision loss results when chorioretinal atrophy extends into the macula. The NVAMD phenotype is the minority, comprising approximately 15% of patients with AMD; however, 80% of severe vision loss in AMD is the result of NVAMD. Neovascular AMD is the most common cause of severe vision loss in individuals over 50 years and central vision loss in individuals over 65 years of age in developed countries (Shao et al, 2016, Lois, 2004). In a large epidemiological study combining data from the US, the Netherlands, and Australia, the prevalence of NVAMD was found to be 0.88%, 0.72%, and 1.20%, respectively (Lois, 2004). The number of AMD patients is predicted to grow significantly with aging populations to nearly 300 million people by 2040 (Mitchell et al, 2018).

Neovascular AMD is characterized by the development of pathological choroidal neovascularization (CNV), in which abnormal and leaking blood vessels cause distortion and/or damage to the macular region. Clinically, this phenomenon is characterized with a combination of findings such as the presence of edema, fluid, blood and hard exudates affecting the various layers of neurosensory retina, and/or retinal pigment epithelium (RPE) (Lois, 2004). Research on AMD has focused on RPE dysfunction, a critical pathological player that leads to advanced disease and vision loss, whereas mechanisms of endothelial dysfunction in choroidal neovascularization remain elusive (Yeo et al, 2019). Exudation secondary to CNV can lead to rapid deterioration in central vision (within weeks to months if untreated).

A growing body of literature is providing evidence that the pathogenesis of choroidal neovascularization may arise from initial structural changes in the vasculature (Blaauwgeers et al, 1999; Marneros et al, 2005; Biesemeier et al, 2014; Seddon et al, 2016; Chirco et al, 2017).

Wong et al (2016) have presented a comprehensive review of the epidemiology, detailed risk factors, and clinical manifestations of typical choroidal neovascularization. Mechanisms that could lead to common vessel wall pathology in typical choroidal neovascularization include impaired extracellular matrix metabolism (Nakashizuka et al, 2008; Jones et al, 2011), involvement of the high-density lipoprotein pathway (Liu et al, 2014), choroidal vascular hyperpermeability associated with genetic polymorphisms ARMS2 A69S (rs10490924) and CFH (rs1329428) (Yoneyama et al, 2016), and choroidal venous congestion leading to thickened choroid (Chung et al, 2013).

Investigational treatments for NVAMD are currently dominated by variations of anti-VEGF treatments that aim to improve visual outcomes and reduce treatment burden in NVAMD (Al-Khersan et al, 2019). The long-term utility of these treatments is yet to be demonstrated.

A number of approved anti-VEGF agents are used to treat NVAMD. These include ranibizumab (Lucentis®), aflibercept (Eylea®), brolucizumab (Beovu®) and faricimab (Vabysmo®). Bevacizumab is also commonly used globally in an off-label manner for treating NVAMD. While anti-VEGFs are effective at mitigating exudation associated with CNV and preserve vision in some

patients with NVAMD, there still remains a large unmet need in terms of treatment burden and clinical outcomes. Only one third of patients treated with anti-VEGF therapy gain more than 3 lines of vision, and only 40% maintain vision of 20/40 or better (Heier et al, 2012). As discussed under the disease background for DME (Section 1.1), EYE103 is a potential novel therapy in the activation of FZD4/LRP5/β-catenin signaling in endothelial cells which can promote or restore vascular barrier function by mimicking Norrin activity and thus represents a novel therapeutic opportunity for the treatment of retinal vascular diseases driven by BRB dysfunction (Chidiac et al, 2021). Given the prominent role of leakage in NVAMD, reconstituting the BRB to reduce exudation via agonism of the Wnt pathway is a promising therapeutic approach.

### 1.3. CCI

CCI

[redacted]

### 1.4. CCI

#### 1.4.1. CCI

CCI

[redacted]

CCI



### 1.4.2. CCI

CCI



CCI

[redacted]

### 1.5. CCI [redacted]

CCI

[redacted]

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Objective

The objectives of the study are to evaluate the safety, tolerability, preliminary efficacy, and pharmacokinetic (PK) profile of intravitreal injection (IVT) of EYE103.

## 2.2. Safety Endpoints

The safety endpoints for the study are adverse events (AEs), serious adverse events (SAEs), and laboratory assessments throughout the study

## 2.3. Efficacy Endpoints

### 2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint for the study is the following:

- Mean change in best-corrected visual acuity (BCVA) using the standardized ETDRS (early treatment of diabetic retinopathy study) chart from baseline to Week 12 in the study eye of the participants diagnosed with DME or NVAMD.

### 2.3.2. Other Efficacy Endpoints

The other efficacy endpoints for the study are the following:

- Early treatment of diabetic retinopathy study BCVA response, defined as a gain from baseline in the study eye by 15 or more letters (DME and NVAMD participants) at Week 12
- Mean change in retinal central subfield thickness (CST) from baseline in the study eye based on spectral domain optical coherence tomography (SDOCT) (DME and NVAMD participants) at Week 12
- Percentage of patients with loss of vision from baseline in the study eye by 15 or more letters (DME and NVAMD participants) at Week 12

## 2.4. PK Endpoints

The PK endpoints for the study are the following: time of maximum serum concentration ($T_{max}$), maximum serum concentration ($C_{max}$), area under the curve from time zero to last quantifiable timepoint ($AUC_{last}$), area under the curve from time zero extrapolated to infinity ($AUC_{inf}$), percent $AUC_{inf}$ extrapolated ($AUC_{ext}$), clearance (CL), volume of distribution at steady state ($V_{ss}$), and terminal elimination half-life ($t_{1/2}$).

## 2.5. Other Endpoints

The other endpoint for the study is anti-drug antibody (ADA) (immunogenicity) blood levels at various timepoints pre- and post-injection.

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design

### 3.1.1. Part 1: Multiple Ascending Dose

In this portion of the study, which will only be conducted in the USA, 4 cohorts, each comprised of 3 participants, will receive IVT EYE103 at 4 dose levels in ascending order (0.05, 0.15, 0.48 and 0.8 mg) in an open-label and uncontrolled design. The participants will be comprised of a mixed population who will be comprised of: (1) naïve participants with DME who will receive EYE103 as monotherapy, (2) participants naïve to anti-VEGF with NVAMD, or (3) anti-VEGF experienced participants with NVAMD. Participants with NVAMD will receive EYE103 in combination with aflibercept, if naïve, or their previously utilized anti-VEGF agent, if experienced (2 mg aflibercept, 0.5 mg ranibizumab, or 1.25 mg bevacizumab), given 30 minutes apart by IVT. There will be no restriction on the proportion of participants enrolled from each of the 3 populations. The first 3 participants will be enrolled into Cohort 1 and, on Day 1, will receive an IVT injection of 0.05 mg of EYE103 in the eye selected as the study eye (i.e., the eye with the

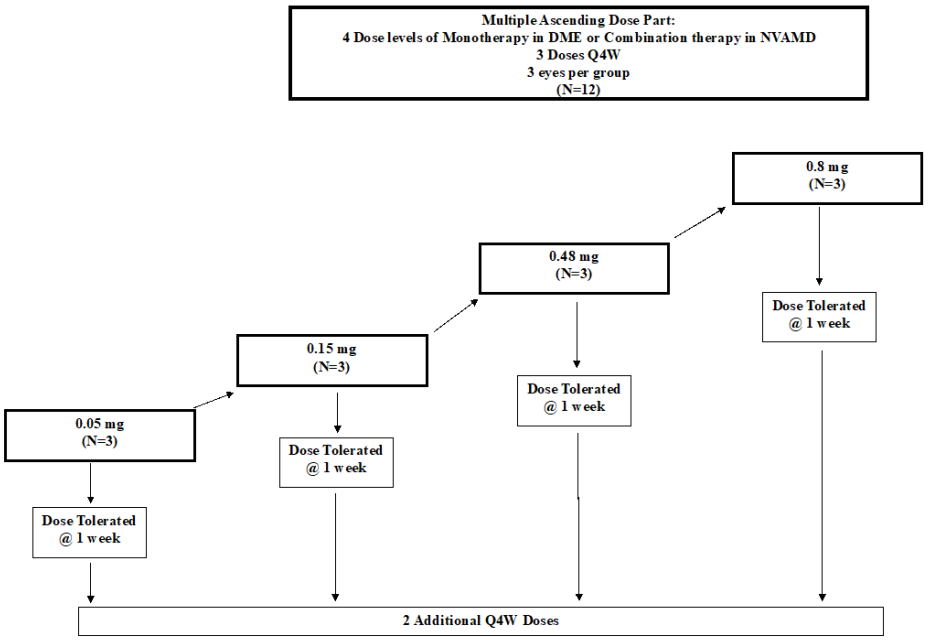
worst vision). The study site will call each participant the following day (24 ±4 hours) to confirm whether there have been any adverse signs or symptoms. Participants will return 1 week later (Day 8 ±1 day after the first dose) to be examined for any adverse changes. Participants will also be instructed to call the study site at any time between study visits to discuss any concerns about their treatment. Participants will return at Week 4 (i.e., 4 weeks after the first injection) to receive their second dose. The study site will again call each participant the following day (24 ±4 hours) to confirm that there have been no adverse signs or symptoms, and the participants will be instructed to call the site if there are any concerns about their treatment. The participants will then return at Week 8 for their final injection and again will receive a telephone call from the study site the following day (24 ±4 hours). All participants will return for their final study assessments at Week 12 (or Week 24 for the extended treatment participants).

Participants in Cohort 2 will receive their first IVT injection of 0.15 mg of EYE103 once all 3 participants in Cohort 1 have received their first doses of EYE103 and have completed their Day 8 visits confirming safety. Cohort 2 participants will then receive their second and third injections following the identical protocol to Cohort 1 and will be required to attend their follow-up visit at Week 12 (or Week 24 for the extended treatment participants).

Similarly, participants in Cohorts 3 and 4 (the 0.48 mg and 0.8 mg doses respectively) will commence dosing when all 3 participants in the preceding cohort have received their first dose and completed their Day 8 visits confirming safety. Participants in Cohort 3 will receive the high mid-dose of EYE103, and participants in Cohort 4 will receive the high dose of EYE103. Participants in Cohorts 3 and 4 will follow the identical schedules as Cohorts 1 and 2, will receive their second and third doses of EYE103 at Weeks 4 and 8, and will complete their follow-up visit at Week 12 (or Week 24 for the extended treatment participants).

If at any time a participant experiences a dose-limiting toxicity (DLT) (defined as an AE with a severity ≥ Grade 3 on the Common Terminology Criteria for Adverse Events (CTCAE) scale for systemic DLTs in Appendix D, or as defined in Appendix E for ocular DLTs), then the data safety monitoring board (DSMB) will be informed and the cohort at which the DLT occurred will be expanded to include 3 more participants (to a total of 6 participants). Any enrollment of participants at a higher dose level than that at which the DLT occurred will be put on hold until resumption of enrollment is agreed and the DSMB informed. If a second DLT occurs at the same dose level, then all treatments at that dose level and higher will be halted, and the dose below that dose level will be considered as the maximum tolerated dose (MTD). The sponsor may also choose to add an additional 3 participants to any dose cohort to further assess the drug profile. In addition, participants in both Part 1 and Part 2, at up to 5 selected sites, may elect to receive 3 additional injections at Weeks 12, 16, and 20 with a follow-up visit at Week 24.

**Figure 1: Part 1: MAD Study Schematic**




Note: If at any time a participant in any of the dose group cohorts experiences a DLT, defined as a related AE with a severity ≥ Grade 3 on the CTCAE scale, then the DSMB will be informed and the cohort at which the DLT occurred will be expanded to include 3 more participants (to a total of 6 participants). Any enrollment of participants at a higher dose level than that at which the DLT occurred will be put on hold until resumption of enrollment is agreed and the DSMB is informed. If a second DLT occurs at the same dose level, then all treatments at that dose level and higher will be halted, and the dose below that dose level will be considered as the MTD.

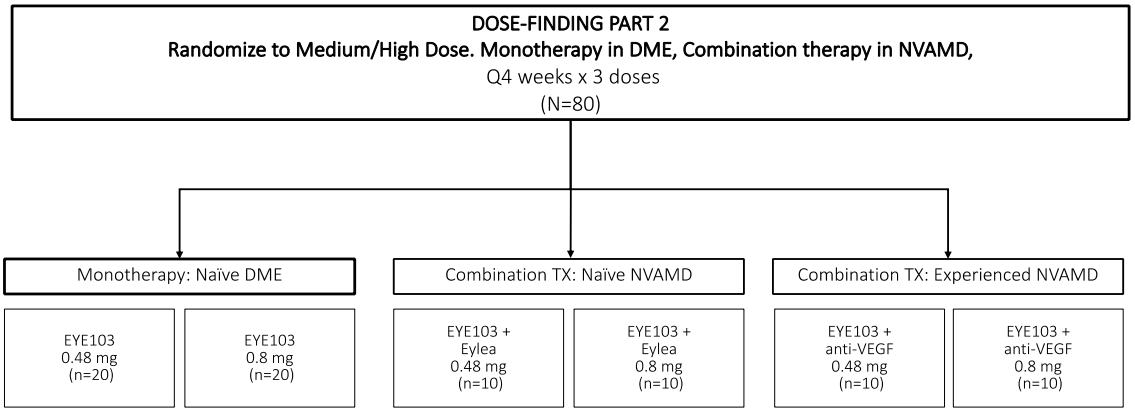
### 3.1.2. Part 2: Dose-finding Efficacy

Once the last participant in the MAD portion of the study has received their first dose, completed their Day 8 safety visit, and the MTD either has been determined or declared as not having been reached at the doses tested, two of the four doses will be selected for inclusion in this dose-finding study, based on safety and any preliminary efficacy signals observed.

The dose-finding part of the study will be randomized, and the dose-level masked to both the participants and study site personnel, including the physician responsible for assessing safety and efficacy. The exception will be the site personnel preparing the syringes for injection who will be unmasked. If this is performed by a physician, then two physicians will be required for the study at that site – one masked for undertaking study assessments and one unmasked for preparing the study medication. The dose-finding part of the study will be divided according to whether the participants are naïve DME participants, naïve NVAMD participants, or experienced NVAMD participants: 2 cohorts, each consisting of 20 naïve DME participants will be randomized (1:1) to 1 of the 2 selected doses of EYE103, which they will receive as monotherapy; 2 cohorts, each consisting of 10 naïve NVAMD participants, will be randomized (1:1) to 1 of the 2 selected doses of EYE103, which will be given in combination with 2 mg aflibercept; and 2 cohorts, each consisting of 10 experienced NVAMD participants, will be randomized (1:1) to 1 of the 2 selected doses of EYE103, which will be given in combination with their previously utilized anti-VEGF agent (2 mg aflibercept, 0.5 mg ranibizumab, or 1.25 mg bevacizumab), given 30 minutes apart by IVT. Enrollment may be directed into specific disease cohorts at the sponsor's

discretion. Allocation into the groups will always be performed using 1:1 randomization within each disease cohort. In addition, participants in both Part 1 and Part 2 at up to 5 selected sites, may elect to receive 3 additional injections at Weeks 12, 16, 20 with a follow-up visit at Week 24.

**Figure 2: Part 2: Dose-Finding Study Schematic**




There will be a small sub study conducted in a subgroup of US participants: 20 participants will be consented separately for the sub study and those that agree will each be provided with iCare HOME2 tonometers (additional detail provided in Section 3.2).

## 3.2. Study Procedures

All participants will be screened within 28 days prior to treatment and will have physical examinations and vital signs collected to exclude any abnormalities that would preclude their participation in the study. A physical examination will be repeated at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit, and vital signs, together with AEs and concomitant medications, will be performed/recorded at all study visits.

For the MAD part of the study only, electrocardiograms (ECGs) will be performed at Screening and 3 days (±1 day) after the first and third injections, and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. Once an initial diagnosis of DME or NVAMD is determined, participants will undergo the following assessments to confirm eligibility: full medical and ocular history, ETDRS BCVA, biomicroscopy, fundoscopy, intraocular pressure (IOP) measurement, SDOCT, FA, and color fundus photography (CFP), and these will be repeated at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. In addition, for sites with OCTA capability, OCTA will be performed at the same timepoints that SDOCT is performed.

All ophthalmology assessments will be performed on both eyes throughout the study. Eligibility based on FA, CFP, and SDOCT (OCTA, if available) will be determined by the independent reading center (IRC). Participants will also receive a telephone call from study site personnel (24 ±4 hours) after each injection to confirm that no untoward effects have occurred following the IVT. However, participants may choose to return to the study site the following day for an eye exam and IOP measurement if that is their preference.

For the MAD part of the study only, all participants will return to the study site for biomicroscopy, fundoscopy, SDOCT (OCTA, if available), and IOP measurements 1 week after the first injection (Day 8) in each of the 4 dose cohorts.

In the dose-finding part of the study only, participants in the sub study will be consented separately, and those that agree will each be provided with iCare HOME2 tonometers, with which they will be instructed (after training) to record the IOPs of both eyes twice a day 12 hours (±1 hour) apart (preferably 8:00 am and 8:00 pm) for 1 week following each injection. In addition, participants in the sub study will return to the study site (24 ±4 hours) after the first injection for IOP measurement.

In both the MAD and dose-finding parts of the study, BCVA, biomicroscopy, fundoscopy, IOP, SDOCT, and OCTA will be repeated prior to each treatment at the Week 4 and 8 visits, and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. In addition, FA and CFP will be repeated at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. Concomitant medications and AEs will be recorded at all visits and elicited during the safety follow-up telephone calls. Clinical laboratory tests will include overnight fasting serum chemistry, lipid panel, hematology, HbA1c (Screening only) and coagulation profile. All women of childbearing potential will have a serum pregnancy test at Screening and a urine pregnancy test prior to each dose and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. The clinical laboratory tests will be performed at Screening and again at the Week 12 (or Week 24 for the extended treatment participants) follow-up visit. An additional visit one week after the first dose (Day 8 ±2 days) in the dose-finding study will assess BCVA, SDOCT (and OCTA if available), IOP, AEs and concomitant medications.

In the MAD part of the study only, comprehensive blood sampling for PK analyses will be collected at the following time points: within 30 minutes before and 4 hours (±1 hour) following the first dose (Day 1), 3 days (±1 day) after the first dose (Day 4), Day 8 (±3 days), within 30 minutes prior to the second dose at Week 4 (±3 days), within 30 minutes prior to, and 4 hours (±1 hour) after, the third dose (Week 8), 3 days (±1 day) and 8 days (±3 days) after the third dose, and finally again at the Week 12 follow-up visit.

In both the MAD and dose-finding parts of the study, samples for ADA analyses will be collected prior to dosing on treatment days on Day 1, Weeks 4 and 8, and again at Week 12 (or Week 24 for the extended treatment participants). In the dose-finding part of the study, samples for PK analyses will be collected at the same time points as those for the ADA samples. The exact time and date of sample collection must be recorded according to the instructions in the Laboratory Manual, which will also provide details on the collection method and volumes for all PK and ADA samples. Participants who elect to receive 3 additional study treatments at Weeks 12, 16 and 20 will undergo the study assessments outlined in Section 6.3 and will undergo the same follow-up assessments at the Week 24 visit as they would otherwise have had at the Week 12 visit.

In addition, the following will be recorded for all participants at approximately 12 weeks after each participant's 4-week follow-up visit: a retrospective patient chart review of all AEs and Con Meds, VA, and any CST measurements from the time between their Week 12 visit and the 24-week timepoint (for participants who receive a total of 3 study treatments). A retrospective chart review of the same parameters will also be made for the participants who agree to 3 additional treatments for the period between their Week 24 follow-up visit and Week 36.

# 4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

## 4.1. Number of participants

The study plans to enroll approximately 92 participants (approximately 12 in the MAD part and approximately 80 in the dose-finding part).

## 4.2. Number and Location of Study Sites

The study is planned to occur in approximately 50 sites in Argentina, Israel, the UK, and the US.

## 4.3. Participant Eligibility Criteria

### 4.3.1. General Inclusion Criteria

Participants must:

1. Be willing and able to understand the study procedures and risks involved and provide written informed consent before the first study-related activity
2. Be male or female ≥ 18 years of age
3. If female, have a negative serum pregnancy test at Screening and further negative urine tests immediately before each dose of study medication if the participant is a female of childbearing potential (including those with <2 years since the onset of menopause, amenorrhea for <1 year, or not surgically sterile); such participants must agree to use an acceptable method of contraception (see Appendix F) for 30 days after the last dose of study medication.
4. If male, be surgically sterile for at least 6 weeks, or agree to use an acceptable method of contraception, such as a condom, and a second highly effective method of contraception (see Appendix F) from Screening up to and including 30 days after the last dose of study medication

### 4.3.2. DME-Specific Inclusion Criteria

Participants must:

1. Have Type 1 or Type 2 diabetes mellitus and a HbA1c of ≤12%
2. Have a BCVA ETDRS letter score between 70 and 35 in the study eye
3. Have a decrease in vision in the study eye determined by the Investigator to be primarily the result of DME
4. Be treatment-naïve with vision loss in the study eye, and center involving DME diagnosed within 9 months of Screening
5. Have a CST of ≥ 350 µm in the study eye on SDOCT as determined by the IRC at Screening

### 4.3.3. DME-Specific Inclusion Criteria for Extended Treatment

2. Any DME participant with a significantly positive anatomic response at their 4-week follow-up visit i.e. >90% resolution of excess retinal fluid on SDOCT and with prior approval of the sponsor

### 4.3.4. NVAMD-Specific Inclusion Criteria

Participants must:

1. Be ≥ 50 years of age
2. Have a BCVA ETDRS letter score between 70 and 35 in the study eye
3. Have either previously treated (experienced) or untreated (naïve) active subfoveal CNV or juxtafoveal CNV (with the lesion 1-199 μm from the fovea) with foveal involvement (demonstrated by leakage on FA and/or IR fluid or SRF on SD-OCT) that is secondary to NVAMD where the total area of the lesion (including blood, neovascularization, and scar/atrophy) is ≤ 6 disc areas (DA), of which at least 50% must be active CNV
4. Foveal thickness ≥ 350 μm in the study eye on SDOCT as determined by the IRC at Screening
5. Be treatment-naïve with vision loss in the study eye secondary to NVAMD diagnosed within 2 weeks prior to the Day 1 study treatment (The **maximum** screening period for these participants is, therefore, 14 days)

   **OR**

   Have been diagnosed with NVAMD within the past 16 weeks and have received 3 anti-VEGF injections within the previous 14 weeks prior to Screening

### 4.3.5. NVAMD-Specific Inclusion Criteria for Extended Treatment

1. Any NVAMD participant receiving combination therapy with anti-VEGF and with prior approval of the sponsor

### 4.3.6. General Exclusion Criteria

Participants must not:

1. Be pregnant or breastfeeding
2. Have a history of cataract surgery and/or minimally invasive glaucoma surgery (MIGS) in the study eye within 3 months of Screening
3. Have had Yttrium-Aluminum Garnet (YAG) laser capsulotomy in the study eye within 2 months of Screening
4. Have had Pan-retinal Photocoagulation (PRP) or focal thermal laser photocoagulation in the study eye within 3 months of Screening
5. Have tractional retinal detachment in the study eye
6. Have uncontrolled glaucoma (defined as IOP ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye
7. Have had glaucoma-filtering surgery (trabeculectomy or tube shunt) in the study eye

8. Have any history of retinal detachment or treatment or surgery for retinal detachment in the study eye
9. Have had any use of regional depot steroids or intraocular steroids
10. Have any history of uveitis in either eye
11. Have significant media opacities, including cataract, in the study eye that might interfere with visual acuity, assessment of safety, OCT, or fundus photography
12. Have a cataract in the study eye that in the judgment of the Investigator is expected to require surgical extraction within 4 months of Screening
13. Have aphakia in the study eye
14. Have allergy to fluorescein dye
15. Have had vitrectomy in the study eye
16. Have known or former myopia with a spherical equivalent of >8 diopters
17. Have active retinal disease other than the condition under investigation in the study eye
18. Have any history or evidence of a concurrent ocular condition present in the study eye that. in the opinion of the Investigator, could require either medical or surgical intervention or affect macular edema or alter visual acuity during the study (e.g., vitreomacular traction, epiretinal membrane, other causes of CNV, such as pathological myopia, angiod streaks, presumed ocular histoplasmosis syndrome, and multifocal choroiditis)
19. Have active or suspected ocular or periocular infection or inflammation in either eye at Day 1
20. Currently have evidence of, or a history of, any clinically significant autoimmune, cardiovascular, hematologic, hepatic, metabolic, peripheral vascular, renal, or respiratory disease, which, in the opinion of the Investigator, would exclude the participant from this study
21. Have a known hypersensitivity to any of the components of EYE103 formulation or prior hypersensitivity to monoclonal antibodies (mAbs)
22. Have previously participated in any study of EYE103 (participants in the MAD study may not subsequently enter the dose-finding study)
23. Presence of amblyopia, amaurosis or ocular disorders with BCVA <38 letters (ETDRS testing charts) in the fellow eye at screening

### 4.3.7. DME-Specific Exclusion Criteria

Participants must not:

1. Have macular edema in the study eye considered to be secondary to a cause other than DME (e.g., retinal vein occlusion [RVO], Irvine-Gass syndrome)
2. Have active iris or angle neovascularization or neovascular glaucoma in the study eye
3. Have proliferative diabetic retinopathy characteristics in the study eye, using any of the following features:

a. Any vitreous or pre-retinal hemorrhage
b. Neovascularization at optic disc
c. Neovascularization elsewhere

4. Have structural damage to the center of the macula in the study eye that, in the opinion of the investigator or sponsor, is likely to preclude improvement in BCVA following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, organized hard exudates in the foveal center, or other evidence of chronic disruption of the macular architecture in the study eye

### 4.3.8. NVAMD-Specific Exclusion Criteria

Participants must not:

1. Have had previous thermal subfoveal laser therapy in the study eye
2. Have had previous photodynamic therapy (PDT) with Visudyne in the study eye
3. Have diabetic retinopathy in the study eye
4. Have the presence of significant and large serous pigment epithelial detachments (PEDs) **such as those** with a vertical height of ≥ 400 μm
5. Have the presence of a tear of the retinal pigment epithelium
6. Have a diagnosis of idiopathic polypoidal choroidal vasculopathy (IPCV)
7. Have fibrosis involving the foveal center or measuring more than 25% of the total lesion area and or juxtafoveal or sub-foveal geographic atrophy
8. Have structural damage to the center of the macula in the study eye that, in the opinion of the investigator or sponsor, is likely to preclude improvement in BCVA. This includes atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, organized hard exudates in the foveal center, or other evidence of chronic disruption the macular architecture

## 4.4. Withdrawal of Participants

Every effort will be made to have all participants attend all study visits and receive all doses of the study drug. Participants can voluntarily withdraw from study treatment and from the study completely at any time during the study. Every effort will be made to complete study follow-up procedures if participants terminate the study treatment or discontinue study participation early. If a participant discontinues study treatment or is withdrawn from the study for any reason, the study site must immediately notify the sponsor. The date and reason for discontinuation must be recorded on the electronic case report form (eCRF). Participants who discontinue early will be asked to return to the study site to complete assessments as indicated in Sections 6.1 and 6.2.

In the event that a participant discontinues prematurely from the study because of a treatment emergent adverse event (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or study baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

A participant may withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- An AE, including, but not limited to, an unacceptable toxicity and/or general or specific change in the participant's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- Participant's withdrawal of consent: at any time, a participant's participation in the study may be terminated at his/her request
- Failure of the participant to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits)
- Lost to follow-up: the participant stopped coming for visits, and study personnel were unable to contact the participant
- Pregnancy

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

Note that the term "withdrawal of consent" is used only when the participant no longer wishes to participate in the study and no longer authorizes the Investigators to make efforts to continue to obtain their outcome data.

A decision on replacement of participants who withdraw from the study will be made on a case-by-case basis.

### 4.5. Rescue Treatment For Participants

The participants' welfare is paramount, and the investigator will decide if a participant should be withdrawn from the study and have an alternative therapy administered at any time during the study. This should be considered by the investigator if a subject experiences a ≥ 10 letter loss of vision from baseline with a corresponding increase of ≥ 50 μm in CST between two consecutive visits which are a week or more apart.

### 4.6. Follow-up of Participants with AEs

Any AE that is not resolved by the end of the study or upon discontinuation of the participant's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if available), or is shown to not be attributable to the study drug or procedures.

## 5. TREATMENT OF PARTICIPANTS

### 5.1. Description of EYE103

EYE103 is a humanized trispecific antibody formulated for IVT administration in 10mM histidine, 8.8% trehalose, 0.02 % polysorbate 80 pH5.5 buffer system at a concentration of 16 mg/mL as a sterile aqueous solution and presented in USP Type I 2R glass single-use vials sealed with a chlorobutyl rubber stopper. The product is preservative free and intended for IVT only.

**Administration of EYE103**

EYE103 is formulated as 16 mg/ml and the pharmacist (or designee) preparing the syringes for injection will draw up 50µl into a sterile 1 ml, USP Type I glass syringe fitted with a sterile 27-gauge needle . The 50 µl of the drug product will be administered as described in Appendix B, and the injecting physician must be an experienced ophthalmologist, skilled in administering IVT injections and **must** be pre-approved by the sponsor. When EYE103 is given in combination with anti-VEGF, EYE103 should be injected first, and a minimum 30-minute separation must elapse before the anti-VEGF is injected.

### 5.1.1. Storage, Accountability and Compliance

The drug product should not be used if cloudy or particles are present. EYE103 should be stored refrigerated at 2-8$^{o}$C (see Pharmacy Manual). Access to the study treatment will be limited to authorized site staff only. The temperature of the storage location for EYE103 at the site must be monitored using a calibrated monitoring device and documented.

The pharmacist or other designated individual will maintain records of the amount of EYE103 delivered to the study site and the inventory at the clinic, including the amount of vials used for each participant. Used vials will be kept until drug accountability has been performed by the monitor and approval to dispose of the used vials is given. Unused material should be disposed of at the unit after approval by the Sponsor, per institution policy, and verified by the monitor.

Records should include dates, quantities, batch/serial numbers, expiration dates, the in-clinic temperature log, and any unique code numbers assigned to the drug product and study participants.

## 5.2. Prior and Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary and tabulated.

Any medication that is administered to the participants during the course of the study must be recorded in the eCRF as a concomitant medication. The entry must include the medication name, dose, regimen, route, indication, and dates of use, and it should be made clear whether treatment with the medication had commenced prior to treatment with EYE103.

### 5.2.1. Prohibited Concomitant Medications

The following therapies are expressly prohibited throughout the study: systemic steroids or any other IVT treatment in the study eye.

# 6. CONDUCT OF STUDY AND STUDY VISITS

## 6.1. Conduct of Study: Part 1 MAD Cohorts

### 6.1.1. Screening and Informed Consent

All participants will receive a written informed consent form (ICF) describing this study and be provided with sufficient information to make an informed decision about participating in this study. Additional consent will be required for the subset of participants who agree to participate in the sub study with iCare HOME2 tonometers. Furthermore, an additional written informed consent will be required for participants who elect to receive 3 additional study treatments starting at Week 12.

The Investigator must obtain informed consent of a participant and/or a participant's legal representative prior to any study related procedures. Documentation that informed consent

occurred prior to the participant's entry into the study and of the informed consent process should be recorded in the participant's source documents, including the date. The original ICF signed and dated by the participant and by the person consenting the participant prior to the participant's entry into the study must be maintained in the Investigator's study files and a copy given to the participant. In addition, if the protocol is amended, and it impacts on the content of the informed consent, the ICF must be revised. Participants participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF, signed and dated by the participant and the person consenting the participant, must be maintained in the Investigator's study files and a copy given to the participant.

Appendix A and the sections below describe the procedures that will be performed at each visit.

### 6.1.2. Visit 1 – Screening (Day -28 to Day -1)

After providing written informed consent, the following procedures will be performed (ophthalmology assessments will be on **BOTH** eyes at all visits):

- Eligibility criteria
- Demographic information
- Medical and ophthalmic history
- Complete physical examination
- 12-lead ECG
- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- FA
- CFP
- SDOCT
- OCTA (if available)
- Fasting laboratory assessments (chemistry, lipid panel, hematology, HbA1c [Screening only], coagulation profile)
- Serum pregnancy test (females of childbearing potential only)
- Prior and concomitant medications
- AEs (from time of consent)

### 6.1.3. Visit 2 – Day 1 (1st IVT)

The following procedures will be performed before study injections:

- Confirm Eligibility (based on VA, CST and Fundoscopy below)
- Vital signs

- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK (within 30 minutes pre- and 4 [±1] hours post-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.1.4. Telephone Call – Day 2

The participants will be questioned about any adverse signs, symptoms, or changes to medication that have occurred since the IVT the day before, specifically:

- Concomitant medications
- AEs

### 6.1.5. Visit 3 – Day 4

The following procedures will be performed:

- 12-lead ECG
- Vital signs
- IOP
- Blood samples for PK
- Concomitant medications
- AEs

### 6.1.6. Visit 4 – Day 8 (±3 days)

The following procedures will be performed:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- SDOCT
- OCTA (if available)

- Blood samples for PK
- Concomitant medications
- AEs

### 6.1.7. Visit 5 – Week 4 – Day 29 (±3 days) (2nd IVT)

The following procedures will be performed before study injections:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK (within 30 minutes pre- and 4 [±1] hours post-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their -anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.1.8. Telephone Call – 1 day post Week 4

The participant will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT the day before, specifically:

- Concomitant medications
- AEs

### 6.1.9. Visit 6 – Week 8 - Day 57 (±3 days) (3rd IVT)

The following procedures will be performed before study injections:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)

- Blood samples for PK (within 30 minutes pre- and 4 [±1] hours post-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.1.10. Telephone Call – 1 day post Week 8 (Day 58)

The participant will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT the day before, specifically:

- Concomitant medications
- AEs

### 6.1.11. Visit 7 – Day 60

The following procedures will be performed:

- 12-lead ECG
- Vital signs
- IOP
- Blood samples for PK
- Concomitant medications
- AEs

### 6.1.12. Visit 8 – Week 9 – Day 64 (±3 days)

The following procedures will be performed:

- Vital signs
- IOP
- Blood samples for PK
- Concomitant medications
- AEs

### 6.1.13. Visit 9 – Week 12 – Day 85 (±3 days) Follow-Up or Early Termination Visit

The following procedures will be performed:

- Complete physical examination
- 12-lead ECG
- Vital signs

- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- FA
- CFP
- SDOCT
- OCTA (if available)
- Fasting laboratory assessments (serum chemistry and lipid panel, hematology, coagulation panel)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK and ADA
- Concomitant medications
- AEs

## 6.2. Conduct of Study: Part 2 Dose-Finding Cohorts

### 6.2.1. Screening and Informed Consent

All participants will be consented and screened as described in Section 6.1.1.

### 6.2.2. Visit 1 - Screening (Day -28 to Day -1)

After providing written informed consent, the following procedures will be performed (ophthalmology assessments will be on **BOTH** eyes at all visits):

- Eligibility criteria
- Demographic information
- Medical and ophthalmic history
- Complete physical examination
- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- FA
- CFP
- SDOCT
- OCTA (if available)

- Fasting laboratory assessments (serum chemistry and lipid panel, hematology, HbA1c [Screening only], coagulation panel)
- Serum pregnancy test (females of childbearing potential only)
- Prior and concomitant medications
- AEs (from time of consent)

### 6.2.3. Visit 2 – Day 1 (1st IVT)

The following procedures will be performed before study injections:

- Confirm Eligibility (based on VA, CST and Fundoscopy below)
- Randomization
- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK (within 30 minutes pre-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.2.4. Telephone Call – Day 2

The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.

- Concomitant medications
- AEs

### 6.2.5. Study Visit for Subjects in the iCare HOME2 Sub Study

The participants in the sub study with iCare HOME2 tonometers will be instructed (after training) to record the IOPs of both eyes twice a day 12 hours (±1 hour) apart (preferably 8:00 am and 8:00 pm) for 1 week following each injection. In addition, participants in the sub study will return to the study site on Day 2 (24 ±4 hours after the first injection) for IOP measurement.

### 6.2.6. Visit 3 – Day 8 (±2 days)

The following procedures will be performed before study injections:

- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Concomitant medications
- AEs

### 6.2.7. Visit 4 – Week 4 (±3 days) (2nd IVT)

The following procedures will be performed before study injections:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK (within 30 minutes pre-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.2.8. Telephone Call – 1 day post Week 4

The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the last IVT:

- Concomitant medications
- AEs

### 6.2.9. Visit 5 – Week 8 (±3 days) (3rd IVT)

The following procedures will be performed before study injections:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP

- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK (within 30 minutes pre-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.2.10. Telephone Call – 1 day post Week 8

The participant will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the last IVT:

- Concomitant medications
- AEs

### 6.2.11. Visit 6 – Week 12 (±3 days) Follow-Up or Early Termination Visit

The following procedures will be performed:

- Complete physical examination
- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- FA
- CFP
- SDOCT
- OCTA (if available)
- Fasting laboratory assessments (serum chemistry and lipid panel, hematology, coagulation panel)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK and ADA
- Concomitant medications
- AEs

## 6.3. Conduct of Study for Participants electing to have 3 additional treatments

### 6.3.1. Visit 6 – Week 12 (±3 days)

The following procedures will be performed before study injections:

- Additional informed consent for extended treatment
- Eligibility sponsor approval
- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for PK (within 30 minutes pre-injection)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.3.2. Telephone Call – 1 day post Week 12

The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.

- Concomitant medications
- AEs

### 6.3.3. Visit 7 – Week 16 (±3 days)

The following procedures will be performed before study injections:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)

- Urine pregnancy test (females of childbearing potential only)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.3.4. Telephone Call – 1 day post Week 16

The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.

- Concomitant medications
- AEs

### 6.3.5. Visit 8 – Week 20 (±3 days)

The following procedures will be performed before study injections:

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- SDOCT
- OCTA (if available)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for ADA (pre-dose)
- EYE103 IVT (for NVAMD participants, this will be followed by their anti-VEGF injection no sooner than 30 minutes later and providing IOP has normalized)
- Concomitant medications
- AEs

### 6.3.6. Telephone Call – 1 day post Week 20

The participants will be questioned about any adverse signs, symptoms or changes to medication that have occurred since the IVT.

- Concomitant medications
- AEs

### 6.3.7. Visit 9 - Week 24 (±3 days) - Follow-Up or Early Termination Visit

The following procedures will be performed:

- Complete physical examination

- Vital signs
- Fundoscopy and biomicroscopy
- IOP
- ETDRS BCVA
- FA
- CFP
- SDOCT
- OCTA (if available)
- Fasting laboratory assessments (serum chemistry and lipid panel, hematology, coagulation panel)
- Urine pregnancy test (females of childbearing potential only)
- Blood samples for ADA
- Concomitant medications
- AEs

# 7. OPHTHALMOLOGY ASSESSMENTS

All ophthalmology assessments will be performed at the visits specified in Section 6.

## 7.1. Intraocular Pressure

Intraocular pressure measurements will be performed using applanation tonometry (Goldmann®, Tonopen® or other). For any given participant, the same IOP assessment method will be used for the duration of the study.

## 7.2. Biomicroscopy

Biomicroscopy will be performed with a slit lamp to examine the anterior and posterior chambers of the eye. The examinations will include an assessment of the lids/lashes, conjunctiva, cornea, iris/anterior chamber, lens, and anterior vitreous.

## 7.3. Fundoscopy

The dilated fundus exam will include assessment of vitreous, retina/macula/choroid, and optic nerve.

## 7.4. Best Corrected Visual Acuity

Manifest refraction and BCVA measurement will be performed according to the standard ETDRS refraction and visual acuity testing protocol outlined in Protocol Procedures Manual (PPM). Training and certification for the visual acuity examiners will be provided by an external provider.

### 7.5. Colour Fundus Photography

All fundus photos will be performed using cameras certified by the IRC. The IRC will certify all photographers performing fundus photos before they perform any imaging on participants. The IRC protocol for image acquisition and transfer is included in the PPM. The IRC will determine the eligibility of NVAMD participants for the study based on the FA images, fundus photos, and OCTs submitted at Screening.

### 7.6. Fluorescein Angiography

All FAs will be performed using digital fluorescein photography equipment certified by the IRC. The IRC will certify all photographers performing FA before they perform any imaging on study participants. The IRC protocol for image acquisition and transfer is included in the PPM. The IRC will determine the eligibility of participants for the study based on the FA images, fundus photos, and OCTs submitted at Screening.

### 7.7. Spectral Domain Optical Coherence Tomography

The IRC will certify the SDOCT machine and technician(s) before the study begins at each site. All images will be sent to the IRC for assessment throughout the study and in accordance with the IRC protocol for image acquisition and transfer, which is included in the PPM. The IRC will determine the eligibility participants for the study based on the OCT images submitted at Screening.

### 7.8. Optical Coherence Tomography Angiography

The IRC will certify the OCTA machine and technician(s) before the study begins at each site. All images will be sent to the IRC for assessment throughout the study and in accordance with the IRC protocol for image acquisition and transfer, which is included in the PPM.

## 8. SAFETY ASSESSMENTS FOR ALL PARTICIPANTS

All safety assessments will be performed at the visits specified in Section 6.

### 8.1. Medical History

Medical history will be recorded at Screening. Investigators should document the occurrence, signs, and symptoms of the participant's preexisting conditions, including all prior significant illnesses. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing (Visit 2) are to be regarded as concomitant.

Illnesses first occurring or detected during the study, and/or worsening of a concomitant illness during the study, are to be documented as AEs on the eCRF. All changes not present at randomization or described in the past medical history and identified as clinically significant must be recorded as AEs, and all SAEs that occur from the time of signing the ICF must be reported as described in Section 9.3.

### 8.2. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be measured after the participant has been resting in a sitting position for at least 5 minutes. Whenever possible, blood pressure measurements should be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if deemed clinically significant or if machine/equipment errors occur. Out-of-range respiratory rate, heart rate, or blood pressure measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurement abnormalities must be recorded as AEs.

### 8.3. Physical Examination

A physical examination (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; neurological and musculoskeletal systems) will be performed by a physician at Screening and Week 12. In addition, focused physical examinations to evaluate any change in clinical status will be performed in the event of any new signs or symptoms.

### 8.4. Electrocardiogram

For the MAD part of the study only (Section 6.1), a 12-lead, resting ECG will be obtained and the Investigator will examine the ECG traces for clinically significant signs of cardiac disease that could exclude the participant from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF.

### 8.5. Laboratory Assessments

Clinical laboratory tests will include an overnight fasting serum chemistry and lipid panel, hematology, HbA1c (Screening only), and a coagulation panel. In women of childbearing potential, serum pregnancy tests will be performed at Screening and urine pregnancy tests thereafter.

The analytes and blood collection, sample processing, and shipment are detailed in the PPM and described in more detail in the Laboratory Manual (LM). Blood for safety assessments will be analyzed at a central laboratory facility. Additional tests may be performed at any time during the study as considered necessary by the Investigator.

In addition, blood samples for PK analyses and ADA will be shipped via the central laboratory but analysed by a different vendor. The visits for planned blood samples for PK and/or ADA collection are provided in Section 6.1 (MAD part of the study) and Section 6.2 (dose-finding part of the study); specific timing of sample collections within these visits for PK and/or ADA are outlined in the LM.

All laboratory reports must be reviewed, signed, and dated by the Investigator. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

## 9. SAFETY MONITORING

The safety and tolerability of drug treatment will be assessed through the collection and analysis of AEs and vital signs monitored during the course of the study, and through ECGs (MAD part of the study only), physical examinations, and laboratory tests recorded before treatment commences and again at Week 12. All safety assessments and protocol-specified tests, including occurrence of AEs, intensity/severity, relationship to study drug, and treatment or action taken to resolve the AE, will be performed by qualified study personnel and/or the evaluating physicians who are listed on the Delegation of Responsibilities Log.

For the purposes of safety monitoring, baseline is defined as the value from the last assessment or blood sample taken before the first injection.

## 9.1. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will oversee the safety of the study and make recommendations related to dose escalation, DLTs, and MTD in the study. The DSMB charter for this study describes its roles and responsibilities and identifies its members. The charter also outlines a plan for disseminating study data and can be made available on request.

## 9.2. Definitions of AEs

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a pre-existing condition is considered to be an AE
- Any illnesses with an onset during the trial
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional

The criteria for determining whether an abnormal objective test finding (e.g., laboratory, ECG, X-ray, physical examination) should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires significant additional concomitant drug treatment, or other therapy or intervention
- Test result leads to a change in study dosing or discontinuation of study drug
- Test result is considered to be an AE by the Investigator or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

A clinical diagnosis, rather than the changes in laboratory or other assessments, should be recorded on the eCRF, as appropriate (e.g., anemia versus low hemoglobin value, bundle branch block rather than abnormal ECG).

From the time the participant receives the initial study treatment until the participant completes the study, protocol-related events should be recorded as well. A protocol-related AE is an AE occurring during a clinical study that is not related to the study product but is considered by the Investigator or medical monitor to be related to the research conditions. For example, a protocol--related AE may be an event related to a medical procedure required by the protocol.

## 9.3. Serious Adverse Events

Any adverse experience occurring at any dose that results in any of the following outcomes is classified as a SAE:

- Results in death
- Life threatening (immediate risk of death)
- Results in persistent or significant disability/incapacity (see below for definition)
- Requires participant hospitalization or prolongs participant hospitalization (see below for definition)
- Results in a congenital anomaly/birth defect in a neonate/infant

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A life-threatening AE is any event that places the subject at immediate risk of death from the reaction as it occurred, i.e., it does not include an event that, had it occurred in a more severe form, might have caused death. For example, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is an official inpatient admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported by the Principal Investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery, or other elective procedures). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls in the same category.
- Social admission (e.g., subject has no place to sleep).

Inpatient admission does not include the following:

- Emergency Room/Casualty Department visits
- Outpatient/same-day/ambulatory procedures and observation/short-stay units
- Hospice facilities and Respite care (e.g., caregiver relief)
- Rehabilitation facilities, skilled nursing facilities, nursing homes, custodial care facilities
- Disability is defined as a substantial disruption in a person’s ability to conduct normal life functions.

## 9.4. Adverse Event Recording and Reporting

AEs and SAEs should be reported from the time the participant is consented until 28 days after the participant receives their last dose of study medication, and this will occur at Week 12. Relatedness to study treatment IVT and/or anti-VEGF agents (given in combination) or study procedures is determined by the Investigator. All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents. All AEs and SAEs for participants who are not screen failures will be recorded on the eCRF.

Study Investigators must follow-up on all AEs, SAEs, and other reportable events until the events have resolved, returned to baseline, or in case of permanent impairment, until the condition stabilizes. If, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease, the Investigator must record his or her reasoning for this decision in the participant's source documentation and on the eCRF. Any medication or other intervention necessary for the treatment of an AE must be recorded on the concomitant medication or procedure eCRF.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Relationship to study treatment
- Outcome
- Treatment or action taken

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used.

## 9.5. Classification of Adverse Events

### 9.5.1. Intensity/Severity

All systemic AEs should be graded by Investigators using the CTCAE Version 5.0 (Appendix D). For ocular AEs the following criteria should be used:

- Mild = Aware of sign or symptom but easily tolerated
- Moderate = Discomfort enough to cause interference with usual activity
- Severe = Incapacitating with inability to work or perform usual activity

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a SAE. For example, a headache may be severe in intensity, but would not be serious unless it met 1 of the criteria for SAEs.

### 9.5.2. Expectedness

All AEs considered related to EYE103 and/or additional anti-VEGF agent will be evaluated as to whether they are expected or unexpected and related to EYE103 and/or anti-VEGF agent, the injection procedure, and/or more than 1 of these. Expectedness will be determined by the Sponsor.

- Expected (anticipated): An AE is expected when the nature, severity, or degree of incidence was previously described in the Investigator's Brochure (IB).
- Unexpected (unanticipated): An AE is unexpected when the nature, severity, or degree of incidence was not previously described in the IB.

### 9.5.3. Relatedness

The Investigator will determine the assessment of the causal relationship of the AE/adverse reaction to the study product/anti-VEGF therapy or injection procedure. Adverse events are assessed as related to the intravitreal injection procedure (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops, subconjunctival injection of anesthetic, intravitreal injection), and termed "injection procedure-related", or to the trial drug itself, or concomitant anti-VEGF agent.

The following terms for assessment of the causality to study product or study procedures are to be used:

- Not related: An event that does not follow a reasonable temporal sequence from administration of the study product or procedure, does not follow a known or expected response pattern to the suspect product or procedure and that could be reasonably explained by the known characteristics of the participant 's clinical state.
- Related: An event that follows a reasonable temporal sequence from administration of the study product or procedure, follows a known or expected response pattern to the suspected product or procedure and that could not be reasonably explained by the known characteristics of the participant's clinical state.

### 9.5.4. Outcome

The clinical outcome of an AE will be characterized as follows:

- Recovered/Resolved
- Ongoing
- Death

### 9.5.5. Action Taken with Study Drug

- The action taken with study drug or procedure will be characterized as follows:
- None
- Study product or procedure interrupted
- Study product or procedure discontinued

## 9.6. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor as soon as possible and no later than 24 hours after the Investigator first learns of the event. The SAE form is to be completed and submitted by email to the Sponsor or designate. For initial reports, Investigators should record all case details that can be gathered within the reporting timeframe. Relevant follow-up information should be submitted to the Sponsor as soon as it becomes available and/or upon request. For some events, the Sponsor or designee or the medical monitor may follow up with the site by telephone, fax, electronic mail,

and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the participant's subsequent medical course must be submitted to the Sponsor until the event has resolved or, in case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained.

Serious AE reporting timelines should be followed when reporting a pregnancy or symptomatic overdose.

The SAE report should be sent via e-mail to the email address specified in the Protocol Procedures Manual (PPM).

The site may also contact safety personnel at the phone number specified in the PPM.

Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Sponsor within 24 hours of the change in seriousness criteria; these reports should be submitted using the SAE Report Form.

- If the site personnel need to speak to the Sponsor's Medical Personnel, the contact information is provided in the PPM

The Sponsor may also be contacted at clinical@eyebiotech.com and additional contact information for the Contract Research Organization (CRO) and Sponsor personnel are provided in the accompanying PPM.

# 10. STATISTICS

All statistical analyses will be performed with an exploratory intent. All statistical considerations and analyses will be fully described in the statistical analysis plan (SAP), which will be finalized prior to database lock and un-masking.

## 10.1. Statistical Methodology

### 10.1.1. Randomization

The MAD part of the study will be open-label and uncontrolled. The dose-finding part of the study will be randomized 1:1 to one of two doses selected from the MAD data and will be single masked- to both participants and site personnel, except for the unmasked site personnel preparing the syringes for injection.

### 10.1.2. Description of Populations for Analysis

**Intent-to-Treat (ITT) Population**

The Intent-to-Treat (ITT) population will include all participants who were randomized into the study, irrespective of whether study medication was administered or not. This dataset will be used to report participant disposition and all efficacy analyses.

**Safety Population**

The Safety population will comprise all participants in the ITT population but excluding those who did not receive at least 1 dose of EYE103. This dataset will be employed to analyze the safety endpoints. Participants will be analyzed according to the study medication received for all safety analyses.

## 10.2. Sample Size

The sample size of this study is not calculated to power a statistical comparison of the 2 doses under investigation. However, with 40, 20, and 20 participants treated per dose level in the dose-finding part of the study, large differences between the randomized groups (in terms of safety or efficacy) are likely to be seen, and further investigated if warranted. With the exception of such large differences, the study is conducted with a descriptive intent.

## 10.3. Endpoints

### 10.3.1. Safety Endpoints

Adverse events, SAEs, and laboratory assessments for participants will be monitored and recorded throughout the duration of the study.

### 10.3.2. Pharmacokinetic Endpoints

The following PK parameters will be derived where applicable

- $T_{max}$
- $C_{max}$
- $AUC_{last}$
- $AUC_{inf}$
- $AUC_{ext}$
- CL
- $V_{ss}$
- $t_{1/2}$

## 10.4. Analysis of Safety

Safety assessments will be made at all study visits and both safety and tolerability will be evaluated by assessing the incidence of AEs and the incidence of SAEs.

Adverse events, SAEs, and other findings will be summarized by presenting the percentages of participants with each event for each treatment group and dose cohort. When relevant, the time course of AEs will be presented.

All safety analyses will be presented by dose group. The safety analysis will be conducted on all subjects who had at least one administration of trial drug. Safety analyses will summarize participants by the treatment received.

Summary statistics will be given on the number of subjects for whom the trial medication had to be interrupted or permanently discontinued.

All laboratory data will be listed and values falling outside normal ranges will be identified. Summary statistics (i.e., mean, median, standard deviation, minimum, and maximum) will be presented for all continuous variables.

The safety analysis will summarize all TEAEs using discrete summaries at the participant- and event-level by system organ class and preferred term. TEAEs will be summarized using MedDRA

terms. A TEAE will be defined as occurring on or after the day that treatment is initiated. Treatment-emergent AEs will also be summarized by severity or toxicity grade and relatedness.

## 10.5. Analysis of PK Endpoints

WinNonlin® PK analysis software will be used for noncompartmental analyses (NCA) and descriptive statistic calculations. Pharmacokinetic parameters will be derived from serum concentrations of EYE103 using the actual sampling times. Concentration data and all PK parameters will be listed per participant and summarized descriptively per dose cohort. Additionally, dose proportionality and male to female comparison will be made, if data allows.

Serum concentration vs. actual time plots for each participant, as well as the mean (+/- SD) serum concentration vs. scheduled time profiles for each dose group, will be presented graphically in linear and semi-logarithmic scales.

## 10.6. Analysis of Efficacy Endpoints

The eye with the worse vision will be selected as the study eye. All efficacy analyses will have a descriptive intent. Efficacy analyses will be presented using the ITT populations. Analyses will be performed by population (DME, NVAMD naïve, and NVAMD experienced).

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum), while categorical variables will be summarized as counts and percentages of participants in each category. Results will be presented by study arm as appropriate. For endpoints which are repeatedly measured over time, models for longitudinal data will be used in the dose-finding part, including endpoint information at all visits. In this way, any loss of information is avoided, and within-patient correlation is taken into account.

For the MAD cohorts, primary and secondary endpoints will be tabulated by dose group at 12 weeks.

For the dose-finding part of the study, data will be analyzed together with MAD data for the selected doses. For all continuous efficacy endpoints (except ETDRS BCVA response), the continuous longitudinal data (collected at baseline, Weeks 4, 8, and 12) will be analyzed by using a general linear model (GLM) for correlated data. The estimated mean change from baseline at Week 12 will be tabulated by dose group. The model specifications will be detailed in the SAP. If there are any missing data, the results obtained using GLM are valid under the missing at random (MAR) assumption, i.e., if the probability of missingness depends on the covariates and observed outcomes, but not on the unobserved values of the endpoint. For this reason, no imputations will be done to perform the analyses of the primary efficacy and continuous secondary efficacy endpoints. The changes from baseline will be graphically presented with mean and 95% CI for both doses.

For the categorical endpoint ETDRS BCVA response at Week 12, results will be tabulated by population and dose group.

# 11. DATA HANDLING AND RECORDKEEPING

## 11.1. Data Collection

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the participant's eCRF data

are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The eCRF is the primary data collection instrument for the study. All eCRFs will be kept current to enable the monitor to review the participants' status throughout the course of the study. In order to maintain confidentiality, only the study number and participant number will identify the participant on the eCRF. All data requested on the eCRF must be supported by and be consistent with the participant's source documentation.

All data captured by the electronic data capture (EDC) system will be transferred through an electronic interface into a study database for management, analysis, and reporting. Any other data (e.g., laboratory results) will also be transferred into the database.

The investigator will sign and date the participant eCRF casebook, indicating that the data on the eCRF are an accurate rendition of the participant during the study.

## 11.2. Study Monitoring

The Investigator will permit monitoring, quality audits, and inspections by the government regulatory authorities, and the Sponsor or its representative(s), of all study related documents (e.g., signed ICFs, source documents, regulatory documents, data collection instruments, eCRFs).

Study Monitors hired or contracted by the CRO and approved by the Sponsor, or hired directly by the Sponsor, will be responsible for monitoring the study sites and study activities. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of eCRFs
- Dispensing, storage, and accountability of investigational product
- Source data verification
- AE and SAE reporting
- Essential documents contained within the regulatory binder

For source data verification (i.e., comparison of eCRF entries with participant records), data will be 100% source verified. Member(s) of the Sponsor or their designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's participant population, facilities, and equipment, and to familiarize the Investigator with the protocol.

On site or remote interim monitoring visits and telephone consultations will be performed by the Study Monitor as necessary, to ensure the proper progress and documentation of the study.

## 11.3. Study Documentation and Retention of Records

All study-related correspondence, participant records, consent forms, record of the distribution, and use of all study medication and copies of CRFs should be maintained on file for at least 2 years

after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor or designee to inform the Investigator/institution as to when these documents no longer need to be retained.

### 11.4. Audits and Inspections

Authorized representatives of the Sponsor, or designee, a regulatory authority, an Independent Ethics Committee (EC), or an Institutional Review Board (IRB) may visit any sites to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### 11.5. Quality Control and Quality Assurance

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the Study Monitor.

### 11.6. Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor (or its representative). Amendments specifically involving change to study design, risk to participant, increase to dosing or exposure, participant number increase, addition or removal of new tests or procedures, shall be submitted formally by the Sponsor to regulatory authorities and IRB/ECs for formal approval.

## 12. ETHICS

### 12.1. IRB/EC Review

The study protocol, participant information and consent form, the IB, questionnaires or written instructions to be given to the participant, available safety information, participant recruitment procedures (e.g., study website), information about payments and compensation available to the participants and documentation evidencing the Investigator's qualifications should be submitted to the IRB/EC for review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment. The Investigator must submit and, where necessary, obtain IRB/EC and/or Sponsor approval for all subsequent protocol amendments and changes to the ICF or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB/EC of protocol

deviations or SAEs occurring at the site and other AE reports received from the Sponsor in accordance with local procedures.

Safety updates for EYE103 will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB/EC.

## 12.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, principles set forth in the Declaration of Helsinki (1998 version applicable for study sites in the European Union), ICH Guideline E6 for GCP, Standard Operating Procedures (SOPs) of the Sponsor and any vendors participating in the conduct of the study, and the U.S. Code of Federal Regulations (CFR) Title 21, parts 50, 54, 56, and 312.

Appendix C provides more detail about the Sponsor's commitments to clinical research and to this study.

## 12.3. Participant Confidentiality

Confidentiality of participants' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. The HIPAA regulations require that, in order to participate in the study, a participant must sign an authorization from the study that he or she has been informed of the following:

- What Protected Health Information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the participant's medical records, but the participant will be able to obtain the research records after the conclusion of the study and following publication and/or reporting on clinicaltrials.gov website
- Whether the authorization contains an expiration date
- The rights of a research participant to revoke his or her authorization

In the event that a participant revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

Measures to protect confidentiality will include a unique study identification number that will identify participants on the eCRF, or other documents submitted to the Sponsor. This information will be used in the database for participant identification. Participant names or addresses will not be entered on the eCRF or in the database. No material bearing a participant's name will be kept on file by the Sponsor. Participants will be informed of their rights within the ICF.

## 12.4. Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the Investigator of the results of the study conducted at his/her research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within 15 months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish his/her results from the study, participant to the notice requirements described herein and participant to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor 30 days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional 60 days solely to permit the Sponsor to seek patent protection.

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# APPENDIX A: SCHEDULE OF ASSESSMENTS

## Schedule of Assessments for Part 1: MAD

| Visit # | V1 | V2 | *T1* | V3 | V4 | V5 | *T2* | V6 | *T3* | V7 | V8 | V9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -28 to Day -1** | **D1** | **D2** | **D4** | **D8 ±3 days** | **W4 Day 29 ±3 days** | **1 day post W4** | **W8 Day 57 ±3 days** | **Day 58** | **Day 60** | **W9 Day 64 ±3 days** | **W12 Day 85 ±3 days[e]** |
| **Informed consent** | X | | | | | | | | | | | |
| **Eligibility review** | X | X | | | | | | | | | | |
| **Demographics/ prior meds, medical & ophthalmic history** | X | | | | | | | | | | | |
| **Physical exam** | X | | | | | | | | | | | X |
| **ECG** | X | | | X | | | | | | X | | X |
| **Vital signs** | X | X | | X | X | X | | X | | X | X | X |
| **Fundoscopy/biomicroscopy** | X | X | | | X | X | | X | | | | X |
| **IOP[d]** | X | X | | X | X | X | | X | | X | X | X |
| **ETDRS BCVA** | X | X | | | | X | | X | | | | X |
| **FA** | X | | | | | | | | | | | X |
| **CFP** | X | | | | | | | | | | | X |
| **SDOCT** | X | X | | | X | X | | X | | | | X |
| **OCTA if available** | X | X | | | X | X | | X | | | | X |
| **Laboratory assessments[a]** | X[a] | | | | | | | | | | | X[a] |
| **Pregnancy test[b]** | X[b] | X[b] | | | | X[b] | | X[b] | | | | X[b] |
| **Blood samples for PK[c]** | | X[c] | | X | X | X[c] | | X[c] | | X | X | X |
| **Blood samples for ADA** | | X | | | | X | | X | | | | X |
| **IVT of EYE103 & anti-VEGF[d]** | | X[d] | | | | X[d] | | X[d] | | | | |
| **Concomitant medications** | X | X | X | X | X | X | X | X | X | X | X | X |
| **AEs** | X | X | X | X | X | X | X | X | X | X | X | X |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BCVA = best-corrected visual acuity; CFP = color fundus photos; ECG = electrocardiogram; ETDRS = early treatment of diabetic retinopathy study; FA = fluorescein angiography; IOP = intraocular pressure; IVT = intravitreal injection; OCTA = optical coherence tomography angiography; PK = pharmacokinetics; SDOCT = spectral domain optical coherence tomography; T= telephone call to participant; V = participant visit to study site

[a] Laboratory assessments (HbA1c is only at screening) for safety must be collected after an overnight fast

[b] Pregnancy test will be serum at the Screening Visit and urine on all subsequent days (for females of childbearing potential). If urine sample is positive this should be confirmed by a serum test.

[c] The blood samples on the IVT days for PK will be drawn within 30 minutes before the IVT and 4 hours (±1 hour) after.

[d] There must be at least 30 minute separation and normalisation of IOP between EYE103 and the second anti-VEGF injection in NVAMD participants.

[e] Follow-Up or Early Termination visit

## Schedule of Assessments for Part 2: Dose-finding

| Visit # | V1 | V2 | *T1* | V3 | V4 | *T2* | V5 | *T3* | V6 |
|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -28 to Day -1** | **D1** | **D2** | **D8 ±2 days** | **W4 ±3 days** | **1 day post W4** | **W8 ±3 days** | **1 day post W8** | **W12 ±3 days[e]** |
| **Informed consent** | X | | | | | | | | |
| **Eligibility review** | X | X | | | | | | | |
| **Randomization** | | X | | | | | | | |
| **Demographics/prior meds, medical & ophthalmic history** | X | | | | | | | | |
| **Physical exam** | X | | | | | | | | X |
| **Vital signs** | X | X | | | X | | X | | X |
| **Fundoscopy/biomicroscopy** | X | X | | | X | | X | | X |
| **IOP[d]** | X | X | | X | X | | X | | X |
| **ETDRS BCVA** | X | X | | X | X | | X | | X |
| **FA** | X | | | | | | | | X |
| **CFP** | X | | | | | | | | X |
| **SDOCT** | X | X | | X | X | | X | | X |
| **OCTA if available** | X | X | | X | X | | X | | X |
| **Laboratory assessments[a]** | X[a] | | | | | | | | X[a] |
| **Pregnancy test[b]** | X[b] | X[b] | | | X[b] | | X[b] | | X[b] |
| **Blood samples for PK[c]** | | X[c] | | | X[c] | | X[c] | | X |
| **Blood samples for ADA** | | X | | | X | | X | | X |
| **IVT of EYE103 & anti-VEGF[d]** | | X[d] | | | X[d] | | X[d] | | |
| **Concomitant medications** | X | X | X | X | X | X | X | X | X |
| **AEs** | X | X | X | X | X | X | X | X | X |
| **Sub Study IOP** | | | X | | | | | | |

## Schedule of Assessments for Patients who Elect to receive 3 additional treatments

| Visit # | V6 | *T4* | V7 | *T5* | V8 | *T6* | V9 |
|---|---|---|---|---|---|---|---|
| **Study Week** | **W12 ±3 days** | **1 day post W12** | **W16 ±3 days** | **1 day post W16** | **W20 ±3 days** | **1 day post W20** | **W24 ±3 days[e]** |
| **Informed Consent** | X | | | | | | |
| **Eligibility and Approval** | X | | | | | | |
| **Vital signs** | X | | X | | X | | X |
| **Fundoscopy/biomicroscopy** | X | | X | | X | | X |
| **IOP[d]** | X | | X | | X | | X |
| **ETDRS BCVA** | X | | X | | X | | X |
| **FA** | | | | | | | X |
| **CFP** | | | | | | | X |
| **SDOCT** | X | | X | | X | | X |
| **OCTA if available** | X | | X | | X | | X |
| **Laboratory assessments[a]** | | | | | | | X[a] |
| **Pregnancy test[b]** | X[b] | | X[b] | | X[b] | | X[b] |
| **Blood samples for PK[c]** | X | | | | | | |
| **Blood samples for ADA** | X | | X | | X | | X |
| **IVT of EYE103 & anti-VEGF[d]** | X | | X | | X | | |
| **Concomitant medications** | X[b] | X | X[b] | X | X[b] | X | X |
| **AEs** | X[c] | X | X[c] | X | X[c] | X | X |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BCVA = best-corrected visual acuity; CFP = color fundus photos; ETDRS = early treatment of diabetic retinopathy study; FA = fluorescein angiography; IOP = intraocular pressure; IVT = intravitreal injection; OCTA = optical coherence tomography angiography; PK = pharmacokinetics; SDOCT = spectral domain optical coherence tomography; T= telephone call to participant; V = participant visit to study site

[a] Laboratory assessments (HbA1c is only at screening) for safety must be collected after an overnight fast

[b] Pregnancy test will be serum at the Screening Visit and urine on all subsequent days (for females of childbearing potential). If urine sample is positive this should be confirmed by a serum test.

[c] The blood samples on the IVT days for PK will be drawn within 30 minutes before the IVT.

[d] There must be at least 30 minute separation and normalisation of IOP between EYE103 and the second anti-VEGF injection in NVAMD participants.

[e] Follow-Up or Early Termination visit

# APPENDIX B: DRUG ADMINISTRATION AND INJECTON PROCEDURE

In order to maintain study masking, study products are to be prepared out of eyesight of the participant, and communications between the participant and investigator and unmasked staff are to be limited to those essential to conduct study procedures and reassure the participant.

Administration of the EYE103 and anti-VEGF intravitreal injections, and all associated safety checks, are to be performed by the Treating Investigator, supported by unmasked study staff only.

In NVAMD participants, study medications are to be administered in the following order:

1. If scheduled for administration, EYE103 is given first into the study eye at a dose depending upon the arm that the participant has been allocated to, then:
2. Anti-VEGF (50 µl) is administered into the study eye by IVT. The injection may only be performed once all the safety checks have been satisfactorily completed and IOP has returned to an acceptable level as outlined below.

***Injection Procedure***

Intravitreal injections are to be given using standard technique; however, the procedure must include the following minimum precautions to reduce the risk of complications:

1. In NVAMD participants, EYE103 IVT is to be administered prior to anti-VEGF.
2. The participant's name, study number, and the study eye for injection (OS [oculus sinister, left] or OD [oculus dextrus/dexter, right]) must be checked and physically marked.
3. The drug name and expiry date must be checked by unmasked study personnel and verified by the Treating Investigator.
4. Confirm that the pre-injection IOP has been checked and is not >25 mmHg.
5. The Treating Investigator should wear sterile gloves, use sterile technique, and is recommended to wear a mask throughout the IVT.
6. Administer topical anaesthetic eye drops and/or subconjunctival anaesthesia. The choice of ocular anaesthesia is at the discretion of the Treating Investigator and should be according to the standard of care at the site.
7. Prep the periocular skin (including eyelids) with povidone iodine. Povidone iodine should be instilled into the conjunctival sac. Iodine should be left in contact with the skin and conjunctiva for at least 30 seconds before IVT.
8. The eyelids should be held apart using a lid speculum.
9. The injection should be administered 3.5 mm (pseudophakic eyes) or 4 mm (phakic eyes) from the limbus.
10. The Investigator should confirm that the participant retains at least count fingers vision immediately after the IVT.

11. Retinal artery perfusion pressure should be checked via indirect ophthalmoscopy immediately after each IVT. Compromise of central retinal artery perfusion should be managed as clinically indicated, including by an anterior chamber paracentesis, if necessary, at the discretion of the Treating Investigator.
12. The IOP should be checked about 10-40 minutes after injection, or immediately if there is concern about unexpectedly high IOP. The IOP should be no more than 25 mmHg, and no more than 10 mmHg greater than the pre-injection EYE103 measurement (if administered), before the next IVT can proceed.
13. Steps 1-12 should be repeated for the injection of the anti-VEGF by the Treating Investigator supported by the unmasked team.
14. Participants should be warned what to expect after the injection and advised to contact the site or present immediately if they experience concerning symptoms such as moderate to severe eye pain, worsening vision, or visual field defects.

The anti-VEGF injection must be separated by at least 30 minutes after the injection of EYE103 and the same procedures as described above followed for its administration.

The study participant should not be discharged from the study site until the IOP in the study eye is <30 mmHg. Intraocular pressure lowering therapy may be instituted if considered appropriate by the Treating Investigator.

The IOP measurements that follow the second injection must be undertaken by the Treating Investigator.

Details of study product administration will be recorded in the unmasked source documents and entered into the unmasked section of the eCRF, which will not be accessible to masked study staff. Details captured will include study product details, times of administration, any delay, pause or discontinuation for each of the study products, preparatory medications administered (topical/sub-conjunctival anaesthetic and povidone iodine), and all information concerning safety monitoring, AEs that occurred during product administration and any other concomitant medications or procedures.

# APPENDIX C: SPONSOR'S COMMITMENTS

The Sponsor is committed to:

1. Complying with all applicable health authority regulations governing the conduct of clinical research studies, including the US FDA.
2. Protecting the rights, health, safety and welfare of study participants.
3. Informing the clinical Investigators of any new information about the study which may affect the health, safety or welfare of the participants, or may influence their decision to continue participation in the study.
4. Providing the clinical Investigators with the study protocol, Investigator's Brochure and access to eCRFs on which to document the study evaluation variables for each participant entered into the study.
5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
6. Ensuring equity of consideration among all Investigators in multicenter studies in all matters of publications, meeting presentations, etc.
7. Certifying that IRB/EC approval of the protocol and Investigator's Agreement will be completed prior to treatment at an investigational site.

# APPENDIX D: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Refer to CTCAE, Version 5.0, published November 27, 2017. Online resources are available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60 and include the following documents provided in different formats:

- The file named "CTCAE_5.0_QuickReference_5x7.pdf" provides the most recent release of core terminology and is available as a PDF document in traditional small booklet format.
- The file name "CTCAE_5.0_QuickReference_8.5x11.pdf" provides the most recent release of core terminology and is available as a PDF document in letter-sized format.

# APPENDIX E: DEFINITION OF OCULAR DOSE-LIMITING TOXICITIES (DLTs)

A dose limiting toxicity (DLT) is defined as toxicity that is considered related to study drug. A DLT is further defined as follows:

(a) Ophthalmic DLT

*(i)* Clinical Examination

- Visual acuity: loss of 4 or more lines (≥20 letters), or transition to no light perception (NLP) for subjects whose beginning visual acuity score is less than 20 letters, baseline through week 1. This will not be considered a DLT if the vision loss is due to an event deemed related to the injection procedure by the investigator (e.g., vitreous hemorrhage).
- Clinically significant inflammation: defined as >3+ according to the grading schedule as modified from the Nussenblatt method.
- Tonometry: increase of intra-ocular pressure (IOP) from baseline of ≥15 mmHg on two separate examinations at least one day apart excluding day of injection, despite pharmaceutical intervention.
- Accelerated formation of cataract: progression of one unit from baseline to week 1 defined by the Age-Related Eye Disease Study (AREDS) Lens Opacity Grading Protocol as adapted from the Wisconsin Cataract Grading System where the same observer is used.
- Other severe ocular abnormalities not usually seen in subjects with the condition under study (i.e., DME or AMD).

*(ii)* Fluorescein Angiogram

Significant retinal or choroidal vascular abnormalities deemed related to study drug by the investigator.

(b) Systemic DLT

Grade III (severe), IV (life threatening) or V (death related to adverse event) toxicities as defined in the NCI Common Toxicity Criteria (http://ctep.cancer.gov/forms/ CTCAEv3.pdf), or any significant severe toxicity deemed related to study drug by the principal investigator.

# APPENDIX F: CONTRACEPTION GUIDELINES

The following methods have been determined to be highly effective (< 1% failure rate per year when used consistently and correctly) (Trussell, 2011; Clinical Trials Facilitation and Coordination Group, 2020) and are permitted under this protocol for use by participants and their partners:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments, when this is in line with the preferred and usual lifestyle of the participant;
- Oral, intravaginal, or transdermal combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation;
- Oral, injectable, or implanted progestogen-only hormonal contraception associated with inhibition of ovulation;
    - Note: Progestogen-only "mini-pills" are not considered highly effective methods of contraception for this protocol because inhibition of ovulation is not their primary mechanism of action.
- Intrauterine device (IUD);
- Intrauterine hormone-releasing system (IUS)
- Vasectomy or vasectomized partner, provided that the partner is the sole sexual partner of the female study participant and that the vasectomized partner has received medical assessment of the surgical success;
- Bilateral oophorectomy with or without hysterectomy or tubal ligation at least 6 weeks prior to taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up levels of luteinizing hormone, follicle-stimulating hormone (FSH), and/or estradiol.
    - Female participants who have undergone surgical sterilization by oophorectomy alone will have FSH levels assessed at Screening.