Clinical Research Protocol ONS-5010-008

Study Title:	Safety and Effectiveness of ONS-5010 Compared to Lucentis® in Subjects with Neovascular Age-related Macular Degeneration; NORSE EIGHT
Study Number:	ONS-5010-008 (NORSE EIGHT)
Name of Test Drug:	ONS-5010 (bevacizumab – vikg)
Dose and Formulation:	Recombinant, humanized, anti-human vascular endothelial growth factor monoclonal antibody, administered at a dose of 1.25 mg by intravitreal injection
Indication:	Neovascular AMD
Phase of Development:	Phase 3
IND Number:	138373
ClinicalTrials.gov Identifier:	NCT06190093
Sponsor:	Outlook Therapeutics Inc. 111 South Wood Ave Unit #100 Iselin, NJ 08830
Principal or Coordinating Investigator:	To be appointed before the end of the study
Sponsor's Responsible Head, Clinical Development:	Jennifer M. Kissner, PhD Senior Vice President, Clinical & Regulatory Affairs
Version:	V1.0 19 December 2023 V2.0 17 July 2024

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Signing Time: 7/22/2024 | 8:23:46 AM PDT
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CONFIDENTIAL AND PROPRIETARY INFORMATION

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including the archiving of essential documents.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing Outlook Therapeutics Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles and to abide by the terms of this protocol.

Protocol Number: ONS-5010-008

Protocol Title: **Safety and Effectiveness of ONS-5010 Compared to Lucentis® in Subjects with Neovascular Age-related Macular Degeneration; NORSE EIGHT**

Investigator Signature	*Date*

Print Name and Title

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PROTOCOL SYNOPSIS

TITLE	Safety and Effectiveness of ONS-5010 Compared to Lucentis® in Subjects with Neovascular Age-related Macular Degeneration; NORSE EIGHT
SPONSOR	Outlook Therapeutics, Inc.
NUMBER OF SITES	Approximately 60
RATIONALE	This study will assess the safety and effectiveness of intravitreal injections of ONS-5010 (an ophthalmic specific bevacizumab) compared with ranibizumab intravitreal injections, each administered monthly at Day 0, Week 4, and Week 8, in subjects with neovascular age-related macular degeneration (nAMD).
STUDY DESIGN	This is a multicenter, randomized, masked, controlled study of the safety and effectiveness of intravitreally administered ONS-5010. Eligible subjects will be randomized in a 1:1 ratio to receive 1.25 mg ONS-5010 or 0.5 mg ranibizumab intravitreal injections. Subjects will receive 3 injections at Day 0 (randomization), Week 4 and Week 8 visits.
PRIMARY OBJECTIVE	The primary objectives of the study are as follows: • To evaluate the effectiveness of intravitreal injections of ONS-5010 compared to ranibizumab in preventing vision loss, as measured by the mean change in baseline best correct visual acuity (BCVA) at Week 8

SECONDARY OBJECTIVES	The secondary objectives of the study are as follows:
	• To evaluate the effectiveness of intravitreal injections of ONS-5010 compared to ranibizumab in preventing vision loss as measured by the following:
	  • The proportion of subjects who lose fewer than 15 letters in visual acuity at Week 8 compared with baseline
	  • The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at Week 8
	  • The proportion of subjects who gain ≥15 letters in visual acuity at Week 8 compared with baseline
	  • The mean change from baseline in visual acuity over time up to Week 8

SAFETY OBJECTIVE	The safety objective of the study is to evaluate the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to Week 12
SAMPLE SIZE	The study plans to enroll approximately 400 subjects. The sample size (175 per treatment arm) is adequate for this clinical effectiveness study for the treatment with ONS-5010 (bevacizumab-vikg) versus ranibizumab delivered by monthly intravitreal injections. Group sample sizes of 175 per treatment arm achieve 90% power to detect non-inferiority using a one-sided, two-sample equal-variance t-test. Enrollment of 200 per treatment arm allows for dropouts during the study. The margin of non-inferiority is -3.5. The actual difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.025. The data are drawn from populations with a standard deviation of 10 in both groups.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria** All subjects must meet the following criteria to be eligible for study entry: 1. Signed informed consent 2. Age ≥50 years 3. Active primary subfoveal CNV lesions secondary to AMD in the study eye, as defined in Table 2. Lesions with primary subfoveal CNV with or without a classic CNV component secondary to AMD are permissible. Patients receiving anti-VEGF treatment for AMD in the **fellow eye** are eligible for enrollment in the study.

4. Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA of 35 to 75 letters read (approximately equivalent to 20/32 to 20/200 Snellen) in the study eye. Only one eye will be assessed in the study. If both eyes are eligible, the eye with the most active leakage on fluorescein angiogram and/or the most central retinal edema on OCT will be selected for treatment unless based on medical reasons, the investigator in conjunction with Sponsor eligibility review, deem the other eye to be more appropriate for treatment and study. ETDRS BCVA ≥ 20 letters read (approximately equivalent to 20/400 Snellen) in the fellow eye.
5. As confirmed by the Investigator and independent image reviewer, the study eye must:
    a. Have active leakage on Fluorescein Angiogram involving the fovea
    b. Have edema involving the fovea as measured by central subfield foveal thickness on SD-OCT
    c. Be free of scarring, fibrosis, or atrophy involving the central foveal zone (inner most ring on OCT)

Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for study entry:

Prior/Concomitant Treatment

1. Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
2. Treatment with verteporfin in the non-study eye < 7 days preceding randomization
3. Previous use of approved anti-VEGF or Avastin® in the study eye
4. Previous intravitreal corticosteroid (e.g., intravitreal corticosteroid injection or device implantation) in the study eye
5. Previous subfoveal focal laser photocoagulation in the study eye
6. Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1-month preceding randomization
7. History of vitrectomy surgery in the study eye
8. History of submacular surgery or other surgical intervention for AMD in the study eye
9. Previous participation in any studies of investigational drugs within 1-month preceding randomization (excluding vitamins and minerals)

	Concurrent Ocular Conditions 10. Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either a. Require medical or surgical intervention during the 8-week study period to prevent or treat visual loss that might result from that condition, or b. If allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of BCVA over the 8-week study period 11. Active intraocular inflammation (grade trace or above) in the study eye 12. Current vitreous hemorrhage in the study eye 13. Polypoidal choroidal vasculopathy (PCV) in the study eye 14. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye 15. History of idiopathic or autoimmune-associated uveitis in either eye 16. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye 17. Aphakia or absence of the posterior capsule in the study eye 18. Previous violation of the posterior capsule in the study eye is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) posterior capsulotomy in association with prior posterior chamber intraocular lens implantation. 19. Spherical equivalent of the refractive error in the study eye demonstrating more than –8 diopters of myopia For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should be documented to have not exceeded –8 diopters of myopia, or should not have evidence of high myopia such as staphloma and lacquer cracks 20. Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding randomization 21. Uncontrolled glaucoma in the study eye (defined as intraocular pressure ≥30 mmHg despite treatment with anti-glaucoma medication) 22. History of glaucoma filtering surgery in the study eye 23. History of corneal transplant in the study eye 24. Subfoveal scarring in the study eye as seen on OCT or fundus photography

	Concurrent Systemic Conditions 25. Female subjects who are pregnant, lactating, or planning a pregnancy. Females of childbearing potential must agree to submit to a pregnancy test at screening and agree to use an acceptable method of contraception throughout participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicide or diaphragm with spermicide), hormonal methods (oral contraceptives, implantable, transdermal, or injectable contraceptives), or an intrauterine contraceptive device with a documented failure rate of less than 1% per year. Abstinence may be considered an acceptable method of contraception at the discretion of the Investigator, but the subject must agree to use one of the acceptable birth control methods if she becomes sexually active. Acceptable history of non-childbearing potential may include post-menopausal, hysterectomy, bilateral oophorectomy, tubal ligation, etc. 26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications 27. Current treatment for active systemic infection 28. Known allergy to any component of the study drug or history of allergy to fluorescein, not amenable to treatment 29. Inability to obtain fundus photographs, OCT, or fluorescein angiograms of sufficient quality to be analyzed and graded by the image reviewer 30. Inability to comply with study or follow-up procedures
INVESTIGATIONAL PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	ONS-5010 (a recombinant humanized anti–human VEGF monoclonal antibody), 1.25 mg, intravitreal injection
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Ranibizumab, 0.5 mg, intravitreal injection

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	• Subjects will be screened and, if eligible, randomized within 4 weeks. • Randomized subjects will receive intravitreal injections of ONS-5010 or ranibizumab at D0 (randomization) and Weeks 4 and 8. • The evaluation period concludes at Week 12.
CONCOMITANT MEDICATIONS	**Prohibited Treatments in the Study Eye while on Study Treatment:** • Ranibizumab (Lucentis®) or any ranibizumab biosimilars – other than protocol specified treatments • Bevacizumab (Avastin®) – other than protocol specified treatments • Aflibercept (Eylea®, Eylea HD) or any aflibercept biosimilars • Brolucizumab (Beovu®) • Faricimab (Vabysmo®) • Verteporfin (Visudyne®) • Pegaptanib sodium (Macugen®) • Laser treatment for AMD • Complement inhibitors for geographic atrophy (Syfovre® or iZervay™) in the either eye
PRIMARY EFFICACY ENDPOINT	• The primary efficacy endpoint is the mean change from baseline in ETDRS BCVA letter score at the Week 8 visit

SECONDARY EFFICACY ENDPOINTS	The secondary objectives of the study are as follows:
	• To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss as measured by the following:
	  • The proportion of subjects who lose fewer than 15 letters in visual acuity at Week 8 compared with baseline
	  • The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at Week 8
	  • The proportion of subjects who gain ≥15 letters in visual acuity at Week 8 compared with baseline

EXPLORATORY ENDPOINT	• Mean absolute change from baseline in central subfield foveal thickness at Week 8 and the mean change from baseline in BCVA at Week 4 and Week 12
SAFETY ENDPOINT	The safety outcome measures include the following: • The incidence and severity of ocular adverse events (AEs) • The incidence and severity of non-ocular AEs • Changes and abnormalities in clinical laboratory parameters

	• Changes in vital signs
ANALYSIS POPULATIONS	The following analysis populations are planned: • Safety Population: All enrolled participants who received at least one intravitreal injection of ONS-5010 or ranibizumab will be included in the Safety Population. • Intention-to-treat (ITT) Population: All randomized participants who received at least one injection. • Per-protocol (PP) Population: All participants who are included in the ITT population, who have at least 1 post-dose BCVA score, and who are compliant with all critical study criteria. Subjects with major protocol deviations, identified prior to unmasking the study, will be excluded from the PP population.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CATT	Comparison of AMD Treatments Trials
CFR	Code of Federal Regulations
CK	Creatinine Kinase
CNV	Choroidal Neovascularization
CRO	Contract Research Organization
DME	Diabetic Macular Edema
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HbA1c	Glycated Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HREC	Human Research Ethics Committees
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board

ITT	Intention-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IVT	Intravitreal
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
nAMD	Neovascular AMD
OCT	Optical Coherence Tomography
PBS	Pharmaceutical Benefits Scheme
PCV	Polypoidal Choroidal Vasculopathy
PED	Pigment Epithelial Detachment
PIER	Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age-Related Macular Degeneration
PP	Per Protocol
RBC	Red Blood Cell
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SGOT	Serum Glutamic Oxaolacetic Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
TEAE	Treatment-Emergent Adverse Event
TGA	Therapeutic Goods Administration (Australia)
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
YAG	Yttrium Aluminum Garnet

1 INTRODUCTION

1.1 STUDY PURPOSE

The purpose of this study is to demonstrate that ONS-5010 (bevacizumab-vikg) is noninferior to Lucentis® (ranibizumab) in treating eyes with neovascular age-related macular degeneration (nAMD) when each product is administered monthly.

Previous large, randomized, multi-center, controlled clinical trials evaluating intravitreal bevacizumab (off-label, repackaged Avastin®) in nAMD patients, CATT (Martin et al 2012) and IVAN (Chakravarthy et al 2012), where the test article was tightly controlled, resulted in an efficacy profile non-inferior to Lucentis and similar safety profiles. However, monthly dosed ONS-5010 has not been evaluated against monthly dosed Lucentis.

The quality of Avastin (bevacizumab) acquired from compounding pharmacies for intravitreal injection is inconsistent and the resulting product has been associated with infectious and non-infectious inflammation (Yannuzzi et al 2015), possibly induced by factors relating to the storage or handling of the product (Schargus et al 2020; Gonzalez et al 2012; Palmer et al 2013; Ricci et al 2016). In addition to safety issues, the drug itself may have variable efficacy associated with product aliquoting, handling, and distribution (Kiss 2022; Palmer et al 2013; Yannuzzi et al 2015). Trials have shown that prefilled syringes from compounding pharmacies vary in terms of how much bevacizumab is provided both in volume and concentration, with underdosing being common (Yannuzzi et al 2015); the impact of underdosing, of course, is that patients may appear not to be responding appropriately to treatment, when in fact they simply may be receiving a subtherapeutic dose of the anti-VEGF medication.

Having an additional authorized medicinal product available for the treatment of wet AMD increases authorized treatment options for patients and reduces the risks that would arise from the off-label use of Avastin.

1.2 Risk/Benefit Assessment

NORSE TWO demonstrated significant effectiveness of ONS-5010 in two visual acuity outcomes widely considered by the community of experts as clinically important measurements of visual acuity; in the primary endpoint, 42% of subjects gained three lines (15 letters) of visual acuity, and in a key secondary endpoint, subjects gained 11 letters of mean change from baseline in visual acuity. ONS-5010 also demonstrated highly statistically significant and clinically relevant results on additional secondary endpoints: 69% of subjects gained one-line (5 letters), 57% gained two lines (10 letters) while 94% of subjects lost less than three lines (15 letters) of visual acuity. Furthermore, in a vast majority of patients, 86%, visual acuity remained stable after 1 year. Data derived in NORSE ONE provided proof of biological activity for ONS-5010 consistent with the anti-VEGF class and evidence of effectiveness consistent with the treatment effects observed in the NORSE TWO study population.

The safety of ONS-5010 was assessed and demonstrated adequate safety for its intended use in 4 completed clinical trials. No unexpected safety findings related to ONS 5010 were observed in any of the clinical studies, and the safety results for ONS-5010 were consistent with the known safety profile of ophthalmic anti-VEGF treatments.

Table 1 reflects exposure to ONS-5010 in 341 patients, which constituted the safety population in three completed clinical trials (ONS-5010-001, ONS-5010-002, and ONS-5010-003) and shows frequently reported ocular adverse reactions in ONS-5010 treated patients compared with the control group.

Table 1. Common Ocular Adverse Events in the Study Eye (≥ 2%)

Adverse Reactions	ONS-5010 (N = 341)	Ranibizumab (N = 145)
Conjunctival hemorrhage	5%	3%
Eye pain	2%	1%
Intraocular pressure increased	2%	1%
Retinal hemorrhage	2%	4%
Vitreous floaters	2%	0

Less common ocular adverse reactions reported in the study eye in 1% of patients treated with ONS-5010 were blepharitis, cataract, corneal abrasion, dry eye, punctate keratitis, retinal degeneration, subretinal fibrosis, visual acuity reduced, and vitreous hemorrhage.

Based on a review of TEAEs, SAEs, study drug/study procedure related TEAEs, clinical laboratory assessments, vital sign measurements, and ophthalmic safety findings across the 4 completed studies, the safety profile of ONS-5010, administered monthly for up to 12 months, was similar to that of ranibizumab, dosed less frequently, in adult subjects with nAMD. No unexpected safety findings related to ONS-5010 were observed in any of the clinical studies.

The results of the pivotal clinical study of ONS-5010 demonstrate that the product is effective in the treatment of nAMD and is generally safe and well-tolerated in the intended patient population. ONS-5010 showed highly significant and positive clinical effects across measures of visual acuity, with safety findings as expected following intravitreal injections.

The efficacy and safety results from the clinical trials with ONS-5010 are consistent with those reported from the registration trials for the approved anti-VEGF therapies and the peer-reviewed randomized studies comparing bevacizumab to other anti-VEGF treatments. The data on ONS-5010 presented in this submission reflects a positive benefit-risk profile and supports the efficacious and safe treatment of nAMD with ONS-5010.

The dosing regimen employed in this study will provide participants with treatment equivalent to standard-of-care.

2 STUDY OBJECTIVES

2.1 Primary Objective

This study will assess the efficacy and safety of intravitreal injections of ONS-5010 1.25 mg compared with ranibizumab 0.5 mg injections administered monthly in subjects with primary subfoveal choroidal neovascularization (CNV) with or without a classic CNV component secondary to AMD.

The primary efficacy objective of the study is the mean change in ETDRS BCVA letters read from baseline to Week 8.

2.2 Secondary Objectives

The secondary objectives are as follows:

- To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss as measured by the following:
    - The proportion of subjects who lose fewer than 15 letters in visual acuity at Week 8 compared with baseline
    - The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at Week 8
    - The proportion of subjects who gain ≥15 letters in visual acuity at Week 8 compared with baseline
    - The mean change from baseline in visual acuity over time up to Week 8

2.3 Safety Objective

The safety objective of the study is to evaluate the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to Week 12.

3 STUDY DESIGN

3.1 Study Overview

This is a clinical effectiveness, multicenter, randomized, double-masked, controlled study of the efficacy and safety of intravitreally administered ONS-5010. Approximately 400 subjects with primary subfoveal CNV with or without a classic CNV component secondary to age-related macular degeneration (AMD) will be enrolled. The study will be conducted at approximately 60 study sites.

Eligible subjects will be randomized in a 1:1 ratio to receive 1.25 mg ONS-5010 or 0.5 mg ranibizumab injections. Subjects will receive injections at 3 timepoints, Day 0 (randomization), Week 4, and Week 8.

Subjects will be assessed via study procedures outlined in the Schedule of Study Assessments (Appendix 1).

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline in ETDRS BCVA letter score at the Week 8 visit where BCVA is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity assessment.

5.2 Secondary Efficacy Endpoints

The secondary endpoints include the following:

- The proportion of subjects who lose fewer than 15 letters in visual acuity at Week 8 compared with baseline
- The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at Week 8
- The proportion of subjects who gain ≥15 letters in visual acuity at Week 8 compared with baseline

5.3 Exploratory Endpoint

Mean absolute change from baseline in central foveal thickness at Week 8 and the mean change from baseline in BCVA at Week 4 and Week 12.

5.4 Safety Endpoints

The safety outcome measures include the following:

- The incidence and severity of ocular adverse events (AEs)
- The incidence and severity of non-ocular AEs
- Changes and abnormalities in clinical laboratory parameters
- Changes in vital signs

6 PARTICIPANT SELECTION

6.1 Study Population

Approximately 400 subjects (200 subjects in each arm) with primary subfoveal CNV with or without a classic CNV component secondary to age-related macular degeneration (AMD) will be enrolled.

Written informed consent will be obtained before initiation of any study procedures. Screening evaluations may be performed at any time within the 28 days preceding the day of the first study injection.

6.2 Inclusion Criteria

All subjects must meet the following criteria to be eligible for study entry:

1. Signed informed consent

2. Age ≥50 years
3. Active primary subfoveal CNV lesions secondary to AMD in the study eye, as defined in Table 2. Lesions with primary subfoveal CNV with or without a classic CNV component secondary to AMD are permissible.

   Patients receiving anti-VEGF treatment for AMD in the **fellow eye** are eligible for enrolment in the study.
4. Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA, of 35 to 75 letters read (approximately equivalent to 20/32 to 20/200 Snellen) in the study eye. Only one eye will be assessed in the study. If both eyes are eligible, the eye with the most active leakage on fluorescein angiogram and/or the most central retinal edema on optical coherence tomography be selected for treatment unless based on medical reasons, the investigator in conjunction with Sponsor eligibility review deem the other eye to be more appropriate for treatment and study. ETDRS BCVA ≥ 20 letters read (approximately equivalent to 20/400 Snellen) in the fellow eye.
5. As confirmed by the Investigator and independent image reviewer, the study eye must:
   - Have active leakage on Fluorescein Angiogram involving the fovea
   - Have edema involving the fovea as measured by central subfield foveal thickness on SD-OCT
   - Be free of scarring, fibrosis, or atrophy involving the central foveal zone (inner most ring on OCT)

Table 2: Definitions of Terms Pertaining to AMD Inclusion Criterion

Term	Definition
Active	Defined as: • Leakage on fluorescein angiography consistent with CNV, with associated retinal edema (foveal involving), or pigment epithelial detachment (PED) (foveal involving, verified by OCT) • Geographic atrophy not involving the fovea
Primary	Newly diagnosed and previously untreated
Subfoveal	Including the center of the fovea within the boundaries of the CNV
CNV lesion	A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis
AMD	Clinical and/or angiographic signs consistent with AMD (e.g. drusen, retinal pigment epithelium changes, choroidal neovascularization) with no other likely etiologic explanations for the degenerative changes

6.3 Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for study entry:

Prior/Concomitant Treatment

1. Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
2. Treatment with verteporfin in the non-study eye < 7 days preceding randomization
3. Previous use of approved anti-VEGF or Avastin® in the study eye
4. Previous intravitreal corticosteroid (e.g., intravitreal corticosteroid injection or device implantation) in the study eye
5. Previous subfoveal focal laser photocoagulation in the study eye
6. Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1-month preceding randomization
7. History of vitrectomy surgery in the study eye
8. History of submacular surgery or other surgical intervention for AMD in the study eye
9. Previous participation in any studies of investigational drugs within 1-month preceding randomization (excluding vitamins and minerals)

Concurrent Ocular Conditions

10. Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either
    - Require medical or surgical intervention during the 8 week study period to prevent or treat visual loss that might result from that condition, or
    - If allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of BCVA over the 8 week study period
11. Active intraocular inflammation (grade trace or above) in the study eye
12. Current vitreous hemorrhage in the study eye
13. Polypoidal choroidal vasculopathy (PCV) in the study eye
14. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
15. History of idiopathic or autoimmune-associated uveitis in either eye
16. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
17. Aphakia or absence of the posterior capsule in the study eye
18. Previous violation of the posterior capsule in the study eye is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.
19. Spherical equivalent of the refractive error in the study eye demonstrating more than –8 diopters of myopia. For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should be documented to have not exceeded –8 diopters of myopia, or should not have evidence of high myopia such as staphloma and lacquer cracks
20. Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding randomization
21. Uncontrolled glaucoma in the study eye (defined as intraocular pressure ≥30 mmHg despite treatment with anti-glaucoma medication)
22. History of glaucoma filtering surgery in the study eye
23. History of corneal transplant in the study eye
24. Subfoveal scarring in the study eye, as seen on OCT or fundus photography

Concurrent Systemic Conditions

25. Female subjects who are pregnant, lactating, or planning a pregnancy. Females of childbearing potential must agree to submit to a pregnancy test at screening and agree to use an acceptable method of contraception throughout participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicide or diaphragm with spermicide), hormonal methods (oral contraceptives, implantable, transdermal, or injectable contraceptives), or an intrauterine contraceptive device with a documented failure rate of less than 1% per year. Abstinence may be considered an acceptable method of contraception at the discretion of the Investigator, but the subject must agree to use one of the acceptable birth control methods if she becomes sexually active. Acceptable history of non-childbearing potential may include post-menopausal, hysterectomy, bilateral oophorectomy, tubal ligation, etc.

Adequate contraception methods include:

1. Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable.
2. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
4. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
5. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
6. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. The use of an effective contraception method should continue for 3 months post-injection of the investigational product, in line with the follow-up period of the study.

Because the experimental investigational product in this study may affect an unborn baby, males participating in this study should not father a baby while on this study, and for 4 months following the injection of study medication.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone

level assessment is she considered not of child bearing potential.

26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications
27. Current treatment for active systemic infection

Other

28. Known allergy to any component of the study drug or history of allergy to fluorescein, not amenable to treatment
29. Inability to obtain fundus photographs, OCT, or fluorescein angiograms of sufficient quality to be analyzed and graded by the image reviewer
30. Inability to comply with study or follow-up procedures

7 CONCOMITANT MEDICATIONS

The investigator should instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the eCRF. Protocol specific medications used by a subject during the study are not considered concomitant medications.

No other AMD or anti-VEGF treatments other than ONS-5010 or ranibizumab (as randomized) are permitted in the study eye. Should the fellow eye require treatment during the study with an anti-VEGF, treatment should be applied at the discretion of the Investigator and following the procedures established at the respective site. The fellow eye treatment may occur at any time once the Baseline study eye injection has been administered.

7.1 Prohibited Treatments in the Study Eye while on Study Treatment

- Ranibizumab (Lucentis®) or any ranibizumab biosimilars - other than protocol specified treatments
- Bevacizumab (Avastin®) - other than protocol specified treatments
- Aflibercept (Eylea®, Eylea HD) or any aflibercept biosimilars
- Brolucizumab (Beovu®)
- Faricimab (Vabysmo®)
- Verteporfin (Visudyne®)
- Pegaptanib sodium (Macugen®)
- Laser treatment for AMD
- Complement inhibitors for geographic atrophy (Syfovre® or iZervay™) in the either eye

8 STUDY TREATMENTS

8.1 Method of Assigning Participants to Treatment Groups

Eligible subjects who meet screening inclusion and exclusion criteria will be randomized in a 1:1 ratio to receive either 1.25 mg ONS-5010 or 0.5 mg ranibizumab injections over the study period. Four hundred (400) subjects are currently planned to be randomized for 350 evaluable subjects. When randomized, subjects will be assigned a unique study identification number. Subjects who are randomized but drop out of the study before receiving study treatment will be replaced.

Randomization will be conducted centrally using an electronic randomization module, i.e., an Interactive Web Response System (IWRS). Treatment will be assigned according to a randomization scheme to be generated by an independent, unmasked statistician. The creation and implementation of the randomization scheme will be described in a separate randomization plan to be appended to the Statistical Analysis Plan.

8.2 Masking

There must be a minimum of two investigators per study site to fulfill the masking requirements of this study. At least one investigator will be designated as the evaluating physician, who will be masked to the treatment assignment and will conduct all ocular assessments. Due to the presentation of the compound (color) and needle type required, at least one other investigator will be designated as the injecting physician, who will be unmasked to the treatment assignment and will perform the ONS-5010 or ranibizumab preparation and injection. At least one study coordinator is unmasked for IP preparation if needed, drug accountability and assistance of injection.

In summary:

- BCVA examiner, image photographer, and graders will be masked to study arm
- Subject, evaluating investigator (ophthalmologist), masked study coordinator, Sponsor, masked CRO staff, and additional site staff will be masked to study arm
- Injecting physician and unmasked study coordinators will be unmasked to study arm
- Unmasked data manager will manage drug randomization; all other data managers will be masked

8.2.1 Procedures for Breaking the Masking Prior to Study Completion

Breaking the masking of any previously identified masked party is expressly forbidden except in the event of a medical emergency where the identity of the study drug must be known to properly treat the subject. If breaking the masking is required, then the treatment assignment for the unmasked subject will only be revealed by a qualified designee with approval from the Sponsor's Medical Monitor or designee. In any case of unmasking, the Principal Investigator must record the date and reason for treatment unmasking in the subject's eCRF.

8.2.2 Revealing Randomization and Unmasking

In the absence of a medical emergency, the masked randomization will not be revealed to masked staff until database lock.

8.3 Formulation, Appearance, Packaging, and Labeling of Investigational Product and Control Product

8.3.1 ONS-5010 (Investigational Product)

The investigational product, ONS-5010, is an IgG1 monoclonal antibody specific for VEGF binding. It is a colorless to slightly brown, opalescent liquid.

ONS-5010 will be provided in one of the following formats:

- A labeled carton containing 1 single-use pre-labeled vial containing 7.5 mg bevacizumab in 0.30 mL solution. This provides a suitable amount to deliver a single dose of 0.05 mL containing 1.25 mg of bevacizumab. Each mL of product contains 25 mg bevacizumab. The carton will also contain a blunt filter needle, one injection needle, and one syringe.

or

- A labeled carton containing 1 single-use, pre-labeled, 0.5-cc cyclic olefin polymer pre-filled syringe with overseal closure system containing 7.5 mg bevacizumab in 0.30 mL solution.

Instructions for administration will be provided. There will be no on-site compounding of the investigational product.

8.3.2 Ranibizumab (Control Product)

The control product, ranibizumab [trade name Lucentis] is an IgG1 monoclonal antibody specific for VEGF binding. It is a clear, colorless to pale yellow aqueous solution. Lucentis will be provided at a dose of 0.5 mg. There will be no on-site formulation of the control product.

8.4 Supply of Investigational Product and Control Product at the Site

8.4.1 Dispensing

Sites will be supplied kits for injections of ONS-5010. Each kit will contain 1 single-use pre-labeled 2-cc glass vial or 1 single-use, pre-labeled, 0.5-cc cyclic olefin polymer pre-filled syringe containing 7.5 mg bevacizumab in 0.30 mL solution.

Sites will be supplied commercially available ranibizumab (Lucentis) and subjects will be dosed per protocol.

Temperature indicators that can reliably indicate to the receiving party if the lower or upper temperature limits specified for storage (2-8° C) were exceeded in transit will be placed in each shipment. The staff at each receiving site will document the conditions of each shipment of study drug upon arrival, and immediately transfer the contents into appropriate, refrigerated storage locations. Study drug received with an indication that the specified temperature

conditions were not continuously met in transit will be rejected, placed in quarantine, and the Sponsor notified.

The unmasked injecting Investigator and the unmasked coordinator have the authority to dispense the study drug per the randomization schedule.

8.5 Administration Instructions for ONS-5010 & Ranibizumab

Subjects randomized to ranibizumab will receive 0.5 mg ranibizumab by intravitreal injection at Day 0, Week 4, and Week 8. There will be no modification of study drug dose during this study.

Subjects randomized to ONS-5010 will receive 1.25 mg (in 0.05 mL of solution) at Day 0, Week 4, and Week 8. There will be no modification of study drug dose during this study.

In case the investigator is unable to administer the injection on the day of the assessment for any reason, the injection may be administered within 1 to 3 days (considered as the same visit) following the assessment. Subjects will revert to Standard of Care upon completion of the Week 12 visit.

Subjects randomized will be administered injections in the study eye only. Intravitreal injections must be performed by the injecting physician following the slit lamp examination. A minimum of five minutes prior to injection, a thorough cleansing of the lid, lashes, and periorbital area with 5% povidone iodine for ophthalmic use is conducted and local anesthesia is administered. Immediately prior to the injection 5% povidone iodine for ophthalmic use is applied to the injection site A 30-gauge, ½-inch needle, attached to the provided syringe containing 50 µL of study drug solution, will be inserted through the pre-anesthetized conjunctiva and sclera, approximately 3.5-4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe.

8.6 Safety Plan

Following each injection, subjects will remain at the clinic for 30 minutes (±10 minutes). Gross visual assessment for each subject will be conducted by finger counting within 15 minutes after each injection; with hand motion and light perception tested as necessary. If the initial gross visual assessment after injection was abnormal, this measurement should be conducted again at the 30-minute (±10 minutes) timepoint.

Intraocular pressure will be measured before, and at 30 minutes (±10 minutes) after each injection. If there are no safety concerns in the 30 minutes (±10 minutes) following an injection, the subject may leave the clinic.

If any concern or immediate toxicity is noted, the subject will remain at the clinic and will be treated according to the designated evaluating physician's clinical judgment.

Study drug administration will be temporarily held for subjects who experience certain ocular events or infection events, at the Investigator's discretion. Study drug administration will also be held at a visit if the evaluating physician suspects the lesion in the study eye has converted to predominantly classic CNV.

In the event any subject develops an adverse event in the study eye that is considered by the designated evaluating physician to be severe in intensity, serious consideration should be given to discontinuing the subject from study treatment. The Medical Monitor may be consulted to support evaluation of the risk. Subjects who are discontinued from study treatment will continue to undergo the scheduled assessments. (Appendix 1)

If it is in the investigator's practice to administer artificial tears as the standard of care to subjects after every injection, then this event should not be considered as an AE.

8.7 Investigational Product Accountability

An accurate and current accounting of the dispensing and return of the IP for each participant will be maintained on an ongoing basis by a member of the unmasked study site staff. The number units of IP dispensed and returned by the unmasked Investigator will be recorded on the IP Accountability Record. The unmasked study staff will verify these documents throughout the course of the study.

Unused or outdated vials must be returned, per Sponsor's instructions, where outdated vials will be destroyed.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent must be signed and dated by the participant.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Visit 1 (Screening) and participants will be asked for details of any changes of documented medications at all visits, and at early discontinuation when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, ethnicity, gender, race) will be recorded at Visit 1.

9.1.3 Medical History

Relevant medical history resolved within the past 12 months, including history of current disease, prior exposure to intravitreal anti-VEGF, and information regarding underlying diseases will be recorded at Visit 1.

9.1.4 Review of body systems

A review of body systems will be performed by either the investigator or a sub-investigator who is a physician at Visit 1 and Week 12. New abnormal findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Vital signs include blood pressure (BP) and pulse measurements. After the subject has been sitting for a minimum of 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using a sphygmomanometer. Vital signs will be recorded at every clinic visit.

9.1.6 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated by the electronic data capture program.

9.2 Complete Ocular Examinations

9.2.1 Best corrected visual acuity (BCVA)

ETDRS best-corrected visual acuity (BCVA) will be obtained in each eye separately at all visits. This assessment is to be performed prior to pupil dilation. The number of letters read correctly (for each eye) will be recorded in the appropriate study document. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects.

9.2.2 Intraocular pressure

Intraocular pressure (IOP) will be measured in both eyes at all visits as per the study site's regular practice and recorded in the appropriate study document. IOP measurement will be performed regardless of whether the subject is treated and will be done pre-injection and 30 minutes (±10 minutes) post-injection in both eyes. The measurement method used for a subject must remain consistent throughout the study.

9.2.3 Slit lamp biomicroscopy, including lens grading

Slit lamp exam of the adnexa, conjunctiva/sclera, cornea, anterior chamber, iris, and lens will be obtained on both eyes at all visits. Results from the slit lamp biomicroscopy exam for both eyes will be recorded in the appropriate study document.

Lens grading will be conducted in both eyes at all visits, if either of the participant's eyes are phakic.

9.2.4 Dilated ophthalmoscopy

A dilated examination of the peripheral retina, macula, choroid, optic nerve, and vitreous will be obtained on both eyes at all visits.

9.2.5 Vitreous haze and hemorrhage

During the above dilated ophthalmoscopy examination, additional attention should be directed to scoring the evaluation for retinal tear, retinal detachment, retinal hemorrhage, vitreous hemorrhage density, and vitreous haze. Results from the dilated ophthalmoscopy exam will be recorded on the appropriate study document, along with the vitreous haze grade.

9.2.6 Spectral-domain Optical Coherence Tomography (SD-OCT), Fundus Autofluorescence and Fundus Photography

Spectral-domain optical coherence tomography (SD-OCT) will be used to measure retinal thickness and disease characterization. SD-OCT will be performed pre-injection on both eyes at all visits according to the Imaging Manual. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects.

9.2.7 Fundus Autofluorescence and Fundus Photography

Fundus autofluorescence and seven-field fundus photography will be performed pre-injection on both eyes for each subject as screening, and as per the Schedule of Visits in Appendix 1. Fundus autofluorescence and photography will be performed according to the Imaging Manual. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects.

9.2.8 Fluorescein angiography

Fluorescein angiography will be performed pre-injection on both eyes at screening (Visit 1), Week 12/Study Exit visit, and early discontinuation visits according to the Imaging Manual. Certification of the equipment and examiners for the above examinations at each investigative site will occur prior to evaluation of study subjects.

9.3 Clinical Laboratory Measurements.

Sample handling will be conducted according to the Laboratory Manual.

9.3.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes), and platelet count will be measured as per the Schedule of Study Visits in Appendix 1.

9.3.2 Blood Chemistry Profile

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, glucose, LDH, inorganic phosphorus, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN, and uric acid will be measured as per the Schedule of Study Visits in Appendix 1. If the total bilirubin concentration is increased 1.5 times above the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

9.3.3 Pregnancy Test

A serum pregnancy test will be obtained from female participants who are of childbearing age prior to their participation in the study, and at the Exit visit.

9.3.4 Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained as per the Schedule of Study Visits in Appendix 1, in order to avoid contamination with epithelial cells and sediments and allow proper assessments. A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes, and blood. If the dipstick result is positive for protein, nitrite, leucocytes, and/or blood, the sample will be sent for microscopic analysis of WBC, RBC, and casts.

9.4 Assessment of laboratory and clinical evaluations

In the case where a laboratory assessment is outside the reference range for the laboratory at screening/eligibility, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality.

The assessment may be repeated once. In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study. Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Sponsor personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Sponsor personnel should again be contacted.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Screening)

1. Review the study with the participant (and/or the participant's legal representative) and obtain written informed consent for participation in the study
2. Assign the participant a unique screening number
3. Record demographic data
4. Record relevant medical and surgical history, including diagnosis of complex, rhegmatogenous or chronic retinal detachment, diagnosis date, and prior treatment for retinal detachment or other ocular treatments if applicable
5. Record concomitant medications
6. Perform a review of body systems
7. Perform and record vital signs and record height and weight
8. Collect blood for clinical laboratory tests
9. Collect urine for clinical laboratory tests

10. Perform BCVA in both eyes
11. Perform IOP in both eyes
12. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
13. Perform serum pregnancy test for women of childbearing potential
14. Perform SD-OCT, fundus autofluorescence, & fundus photography in both eyes
15. Perform fluorescein angiography in both eyes
16. Review inclusion/exclusion criteria

10.2 Visit 2 (Day 0)

1. Record any concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Perform BCVA in both eyes
4. Perform IOP pre-injection and before dilation in both eyes
5. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
6. Perform OCT examination in both eyes
7. Prior to randomization, confirm the subject continues to meet all inclusion and no exclusion criteria; ensure the subject's eligibility has been confirmed by the external medical image review and that clinical laboratory tests have been reviewed.
8. Randomize subject using IWRS if they qualify for all the inclusion and exclusion criteria
9. Perform injection of ONS-5010 or ranibizumab in the study eye only
10. Injecting physician to perform finger count, hand motion, light perception within 15 minutes post-injection for study eye only
11. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes
12. Record Adverse events if there are any

10.3 Visit 3 (Day 30±7)

1. Record any concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Perform BCVA in both eyes
4. Perform IOP pre-injection and before dilation in both eyes
5. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
6. Perform OCT examination in both eyes
7. Perform injection of ONS-5010 or ranibizumab in the study eye only
8. Injecting physician to perform finger count, hand motion, light perception within 15 minutes post-injection for study eye only

9. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes
10. Record Adverse events if there are any

10.4 Visit 4 (Day 60±7)

1. Record any concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Perform BCVA in both eyes
4. Perform IOP pre-injection and before dilation in both eyes
5. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
6. Perform OCT examination in both eyes
7. Perform injection of ONS-5010 or ranibizumab in the study eye only
8. Injecting physician to perform finger count, hand motion, light perception within 15 minutes post-injection for study eye only
9. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes
10. Record Adverse events if there are any

10.5 Visit 5 (Day 90±7) / Early termination visit

1. Perform and record vital signs
2. Perform a review of body systems
3. Collect blood for clinical laboratory tests
4. Collect urine for clinical laboratory tests
5. Perform serum pregnancy test for women of childbearing potential
6. Perform BCVA in both eyes
7. Perform IOP before dilation in both eyes
8. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
9. Perform OCT examination in both eyes
10. Perform fundus autofluorescence & fundus photography in both eyes
11. Perform fluorescein angiography
12. Record adverse events if there are any

10.6 Early Discontinuation Visit

If the subject has discontinued early from study drug for any reason, the following procedures should be performed.

1. Record concomitant medication use and concurrent ocular procedures.

2. Perform and record vital signs
3. Perform a review of body systems
4. Collect blood for clinical laboratory tests
5. Collect urine for clinical laboratory tests
6. Perform serum pregnancy test for women of childbearing potential
7. Perform BCVA in both eyes
8. Perform IOP before dilation in both eyes
9. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
10. Perform OCT examination in both eyes
11. Perform fundus autofluorescence & fundus photography in both eyes
12. Perform fluorescein angiography
13. Record adverse events if there are any

10.7 Follow-up visits after early discontinuation of study drug

If the subject has discontinued early from study drug, the following procedures should be performed at the subject's regularly scheduled visits through Week 8.

1. Record concomitant medication use and concurrent ocular procedures
2. Perform BCVA in both eyes
3. Perform IOP before dilation in both eyes
4. Perform OCT examination in both eyes for subjects
5. Record adverse events if there are any

10.8 Unscheduled Visits

If a participant returns to the site prior to their next scheduled study visit for assessment of an adverse event, or at the request of the Investigator, the Unscheduled Visit forms of the eCRF should be completed. Procedures and examinations conducted at the Unscheduled Visit are at the discretion of the Investigator. If the subject is discontinuing at the Unscheduled Visit, the eCRF forms for the Early Withdrawal/Exit Visit and the End of Study Form should be completed rather than the Unscheduled Visit form.

11 ADVERSE EVENT REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a subject administered a pharmaceutical investigational product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the

administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure. Lack of, or insufficient clinical response to the study treatment should not be recorded as an AE. AEs will be recorded from the time the ICF is signed until study termination.

The Investigator and designated staff will probe, via discussion with the participant, the occurrence of AEs during each participant visit and record the information in the site's source documents. Adverse events will be recorded in the subject eCRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment, and relation to the investigational product, or if unrelated, the cause.

AE Relationship to Investigational Product or Procedure

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated or Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

11.2 Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse event
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - is medically significant, i.e., defined as an event that jeopardizes the subject or requires medical or surgical intervention to prevent one of the outcomes listed above

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study treatment). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local IRB/HREC, the site investigator will report SAEs to the IRB/HREC.

All SAEs must be reported within 24 hours of the first awareness of the event. In case of emergency situations, the investigator can email the completed SAE form/ Pregnancy Notification form to safetyreporting@syneoshealth.com, within 24 hours of the first awareness of the event.

12 DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF PARTICIPANTS

12.1 Early Discontinuation of Study Treatment

A participant may be discontinued from study treatment at any time if the participant, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Participant withdrawal of consent
- Participant is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
- Protocol deviation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)
- Lack of efficacy
- If BCVA at any visit has decreased ≥15 letters (3 lines) compared to the baseline BCVA

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All participants who discontinue study treatment should come in for a follow-up visit as soon as possible and then should be encouraged to complete all remaining regularly scheduled visits and follow-up procedures as mentioned in section 10.16 and 18 (Appendix 1)

12.2 Withdrawal of Participants from the Study

A participant may be withdrawn from the study at any time if the participant, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents.

12.3 Replacement of Participants

Participants who withdraw from the study will not be replaced, unless they have not yet received at least one dose of study drug.

13 PROTOCOL DEVIATIONS

A protocol deviation occurs when the participant, investigator, or the Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and/or primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication which may include any other AMD and anti-VEGF treatment in the study eye.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Sponsor will determine if a protocol deviation results in withdrawal of a participant.

When a protocol deviation occurs, it will be discussed with the Investigator and a Protocol Deviation Form detailing the deviation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the files of the Sponsor.

14 STATISTICAL METHODS AND CONSIDERATIONS

14.1 Primary Estimand

The primary clinical question of interest is: What is the treatment effect of ONS-5010 versus ranibizumab at Day 60 on the change from baseline in BCVA score in qualified subjects as defined in entry criteria?

The population of the primary estimand is among subjects aged 50 or higher with primary subfoveal CNV with or without a classic CNV component secondary to AMD. Eligible subjects will be randomized in a 1:1 ratio to receive 1.25 mg ONS-5010 or 0.5 mg ranibizumab injections. Subjects will receive injections at 3 timepoints, Day 0 (randomization), Week 4, and

Week 8. The primary analysis will be executed on the ITT population, including all subjects who are randomized and received at least one injection.

The variable is the change from baseline in BCVA score at Day 60.

Intercurrent events:

Discontinuation from study treatment prior to the completion of the Day 60 efficacy assessment: Treatment policy strategy where results will be used regardless of timing as compared to last dose received. Data collected up to the point of study discontinuation will be included in the analysis.

Use of prohibited concomitant medication: Treatment policy strategy where results will be used regardless of concomitant medications.

Received the wrong treatment (i.e., a treatment other than the randomly assigned treatment): Treatment policy strategy where results will be used regardless of actual dose received. Results will be analyzed according to dose randomized.

The population level summary is the difference between treatment groups (ONS-5010 versus ranibizumab) in mean change from baseline in BCVA score at Day 60, obtained from an analysis of covariance (ANCOVA) model.

Robustness of the estimand will be assessed through sensitivity analyses using alternative methods for handling of missing data.

14.2 Efficacy Analysis

For subjects who have a missing BCVA at the primary efficacy timepoint of 8 weeks, a multiple imputation method will be used for primary and secondary efficacy endpoints. Missing BCVA data will have values imputed using an imputation model that contains the following variables: baseline BCVA value and BCVA values at post-baseline visits, with the multiple imputation stratified by treatment.

In order to further assess the impact of missing data and model assumptions, a number of sensitivity analyses will be performed to support the efficacy analyses including analysis of the last observation carried forward (LOCF), control based multiple imputation, and a completer analysis. Further details are contained in the efficacy analysis section below.

The primary analysis will employ a multiple imputation method that will replace each missing Week 8 BCVA value with a set of plausible values that represent the uncertainty of the correct value based on the observed time matched data at all other visits. The 100 multiple imputed datasets are then analyzed by using standard procedures for complete data and then by combining the results from these analyses using Rubin's Rule (Little and Rubin, 2002). The multiple imputation will be completed by two steps (1) imputing intermittent (non-monotone) missing data using Markov chain Monte Carlo (MCMC) methods to get a monotone missingness data pattern; (2) then using regression method to impute remaining

missing data. Proc MI and Proc MIANALYZE in SAS will be used to generate the datasets and run these analyses. Since this method of imputation assumes that missing data are missing at random (MAR), a sensitivity analysis will be performed to assess whether MAR is a reasonable assumption.

The primary analysis of the mean change from baseline in ETDRS BCVA letter score at Week 8 will be performed using an ANCOVA model with treatment group as a fixed effect and the baseline BCVA as a continuous covariate. Change from baseline will be calculated as the Week 8 value (observed or imputed) minus the observed baseline value. Differences in least squares (LS) means will be estimated for each of the 100 imputed datasets and combined using Rubin's Rule to provide an overall estimate of differences in LS means with corresponding 95% CI. If the lower bound of the 95% CI is greater than the non-inferiority margin of -3.5 letters, then non-inferiority of ONS-5010 can be concluded.

The LS means, standard errors, and LS means difference along with corresponding 95% CIs as obtained from multiply imputed data will be provided by visit. Additionally, as-observed values and as-observed-change will be summarized descriptively by visit.

Secondary efficacy endpoints will utilize the imputed values generated for the primary endpoint. That is, binary responses will be determined from the multiply imputed values described above.

<u>The Proportion of Subjects who Lose ≤ 15 Letters in BCVA at Week 8</u>

The proportion of subjects who lose ≤ 15 letters in BCVA at Week 8 will be compared between treatment arms.

- Binomial proportions will be calculated for each treatment arm for each of the 100 imputed datasets. Analysis between arms will be conducted for each of the 100 imputed datasets with a Mantel–Haenszel (MH) test with adjustment for stratification factor (baseline BCVA ≤ 55, 56 – 65, ≥ 66). For each MI dataset, the COMMONRISKDIFF option in PROC FREQ will calculate the adjusted estimate of the risk difference of success (ONS-5010 minus ranibizumab) over all strata.

- The estimates of the risk differences and their standard errors for all the MI datasets will be input to PROC MIANALYZE to test the alternative hypothesis that ONS-5010 is non-inferior to ranibizumab.

- PROC MIANALYZE will output an overall estimate of the risk difference and corresponding 95% CI. If the lower bound of the 95% CI is greater than the non-inferiority margin for the difference in proportions, then non-inferiority of ONS-5010 can be concluded. The non-inferiority margin will be determined prior to initiating treatment.

Similar analyses will be performed for the remaining secondary endpoints. The non-inferiority testing for secondary endpoints will be conducted in the order listed below, where each successive endpoint analysis will be considered non-inferior only if the prior analysis in the hierarchy is non-inferior.

- The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at Week 8. Note that the direction of this test is reversed. That is, the upper bound of the CI is compared to a positive non-inferiority margin for the difference in proportions.

- The proportion of subjects who gain ≥ 15 letters in BCVA score at Week 8 compared with baseline.

14.3 Sensitivity Efficacy Analyses

Sensitivity analyses will be applied to the primary efficacy endpoint.

To further assess the impact of missing data, the following sensitivity analyses will be performed on the primary efficacy analysis. These analyses will include an ANCOVA with a factor for treatment and study baseline value as a covariate. Pairwise comparisons will be made between treatment groups. Sensitivity analyses to assess the impact of missing data will be evaluated as follows:

1. Last Observation Carried Forward (LOCF) – missing Week 8 BCVA data will be imputed using the last post dose data values.

2. Control-Based Multiple Imputation – for missing Week 8 values for the ONS-5010 treatment group, this method will replace missing values in the ONS-5010 arm based on the observed data for the ranibizumab group. This is a conservative approach, since it assumes that missing ONS-5010 treatment group data would be similar to the control group results subsequent to unavailability, thereby diminishing the difference between the test and control group results. Note that as with multiple imputation under the assumption of MAR, intermittent missing data will first be imputed using MCMC methods to get a monotone missingness data pattern, as these arbitrary missing values are assumed to be MAR.

3. Mixed Model for Repeated Measures (MMRM) – This analysis will be used to determine any potential treatment group differences in the pattern of change in BCVA over time. Using the MIXED procedure in SAS v9.4, change from baseline in BCVA score will be modeled using treatment, visit, and an interaction term of treatment and visit, as fixed effects. The repeated statement will be used to specify a covariance structure to control for within subject variation. The covariance structure (among variance components, compound symmetry, auto-regressive, or unstructured) that results in the lowest Akaike Information Criterion will be used. Furthermore, the LSMEANS statement will be used to provide the LS Means Difference, the associated 95% CI, and p-value comparing treatment arms at each visit.

4. Completer's Analysis – this analysis will include only those subjects who have complete Week 8 results.

14.4 Missing Data

Complete missing or partial dates will be presented in the listings as reported on eCRFs. Missing or incomplete onset dates for AEs and concomitant medications will be imputed as needed in order to determine treatment emergence or determine the prior and concomitant medications.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the first day of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be set to the first day of treatment in order to conservatively report the event as treatment-emergent.

If an AE has a completely missing onset date, then the AE will be considered a treatment-emergent adverse event (TEAE) unless a non-missing stop date indicates otherwise. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

The imputed date of an AE is only used for determining TEAEs and categorizing prior and concomitant medications. The collected partial dates will be reported in the listings.

For subjects who have a missing BCVA at the primary efficacy timepoint of 8 weeks, a multiple imputation method will be used for primary and secondary efficacy endpoints. Missing BCVA data will have values imputed using an imputation model that contains the following variables: baseline BCVA value and BCVA values at post-baseline visits, with the multiple imputation stratified by treatment.

In order to further assess the impact of missing data and model assumptions, a number of sensitivity analyses will be performed to support the efficacy analyses including analysis of the last observation carried forward (LOCF), control based multiple imputation, and a completer analysis. Further details are contained in the efficacy analysis section below.

14.5 Determination of Sample Size

A sample size of 350 participants (175 per treatment arm) is adequate for this clinical effectiveness study for the treatment with ONS-5010 (bevacizumab-vikg) versus ranibizumab delivered by monthly intravitreal injections at Day 0, Week 4, and Week 8. This group sample sizes of 175 achieve >90% power to detect non-inferiority using a one-sided, two-sample equal-variance t-test and allows for drop-outs during the study. The margin of non-inferiority is -3.5. The actual difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.025. The data are drawn from populations with a standard deviation of 10 in both groups. The study will enroll 200 subjects per arm to account for subject drop-outs.

14.6 Demographic and Baseline Characteristics

Participant demographic and baseline variables (age, sex, ethnicity, race, height, weight, and BMI) will be summarized with descriptive statistics. Sex, ethnicity, and race will be summarized

with frequency counts and percentages. Baseline ocular assessments will be summarized descriptively as well.

Pregnancy test results, concomitant medication, and medical history data for each participant will be presented in data listings and summarized descriptively by using frequency counts and percentages.

14.7 Analysis of Safety Endpoints

No formal inferential statistics will be performed on safety assessments. Statistical methods for the safety analyses will be primarily descriptive in nature. Listings and summaries for all safety data will be presented using the Safety Population. Descriptive statistics (mean, SD, median, minimum, and maximum) will be calculated for summaries of continuous safety data and frequency counts and percentages (where appropriate) will be calculated for summaries of discrete/categorical safety data.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and data will be summarized by System, Organ, Class, and preferred term. The number and percent of participants reporting each AE will be summarized descriptively. A participant with two or more AEs within the same level of summarization (i.e., system, organ, class, or preferred term) will be counted only once in that level. The number of AEs reported will also be presented. Adverse events will also be summarized by severity as well as relationship to study treatment. A by-participant AE data listing, including verbatim term, preferred term, system organ class, severity, and relationship to study treatment, will be provided. Separate listings will be generated for SAEs and AEs leading to study/treatment discontinuation.

All hematology, blood chemistry, and urinalysis (continuous variables) parameters will be summarized using descriptive statistics for all study visits assessed, including change from baseline (last pre-surgery value) for all post-surgery assessments. Shift tables will also be generated for each safety laboratory parameter. All laboratory data will be included in the data listings and all test values outside the normal range will be flagged.

All vital sign parameters will be summarized using descriptive statistics by study visit, including change from baseline (last pre-surgery) for all post-surgery assessments. Individual vital sign assessments will be listed for each participant.

Findings of physical examinations will be listed for each participant and summarized descriptively by using count and percentage by study visit.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

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

Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Participants will not be identified by name in

the study database or on any study documents to be collected by the Sponsor (or designee) but will be identified by a site number and participant number.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the eCRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data has been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/HREC, and Regulatory Agency (e.g., FDA,) inspectors upon request. A file for each participant must be maintained that includes the signed Participant Informed Consent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

All study documents (subject files, signed informed consent forms, copies of eCRFs, Study File Notebook, etc.) must be kept secured for a period of fifteen years following the completion of the study.

15.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Data Safety Monitoring Board

A Data Safety Monitoring Board will not be used for this study. The safety of subjects will be monitored by Investigators and by the Medical Monitor on an ongoing basis.

15.8 Participant Confidentiality

In order to maintain participant confidentiality, only a site number, and participant number will identify all study participants on eCRFs and other documentation submitted to the Sponsor. Additional participant confidentiality issues (if applicable) are covered in the Clinical Trial Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/HREC approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the IRB/HRECs are notified within five working days.

16.2 Institutional Review Board / Human Research Ethics Committee

The protocol and consent form will be reviewed and approved by the IRB/HREC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB/HREC in accordance with the standard operating procedures and policies of the IRB/HREC, and the Investigator will keep the IRB/HREC informed as to the progress of the study. The Investigator will obtain assurance of IRB/HREC compliance with regulations.

Any documents that the IRB/HREC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/HREC. The IRB/HRECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/HRECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/HREC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/HREC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/HREC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB/HREC; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form (ICF)

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/HREC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/HREC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/HREC-approved copy of the Informed Consent Form (ICF) to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. Information should be given in both oral and written form and participants (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/HREC, assent from the participant will also be obtained. If a participant is unable to sign the ICF, a legal representative may sign for the participant. A copy of the signed consent form (and assent) will be given to the participant or legal representative of the participant and the original will be maintained with the participant's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights, or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB/HREC review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB/HREC that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB/HREC and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to participants or others (to include amendments and IND safety reports).
9. Seek IRB/HREC approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/participants.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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18 APPENDIX 1. SCHEDULE OF STUDY VISITS

ONS-5010-008							Early Discontinuation[a]	Follow-up visit[m]
	Visit	1	2	3	4	5		
	Week	Up to -4	0	4	8	12		
	Day	–28 to –1	0	30	60	90		
Visit Window (in days)		—	—	±7	±7	±7	—	
Informed consent		X						
Inclusion/exclusion criteria		X						
Medical, surgical, & ocular history[b]		X						
Demographic data		X						
Vital signs		X	X	X	X	X	X	
Review of body systems, including height & weight[f,c]		X				X	X	
Laboratory samples, including serum pregnancy test[d,e,f]		X				X	X	
BCVA[f, g]		X	X	X	X	X	X	X
Slit lamp examination & lens grading[f]		X	X	X	X	X	X	
Intraocular pressure[f,h]		X	X[i]	X[i]	X[i]	X	X	X
Dilated ophthalmoscopy		X	X	X	X	X	X	
Fundus photography[f]		X				X	X	
Fundus autofluorescence[f]		X				X	X	
Fluorescein angiography[f]		X				X	X	
OCT[f]		X	X	X	X	X	X	X
Study Drug Administration[l]			X	X	X			
Post injection safety check[j]			X	X	X			

ONS-5010-008							Early Discontinuation[a]	Follow-up visit[m]
	Visit	**1**	**2**	**3**	**4**	**5**		
	Week	**Up to -4**	**0**	**4**	**8**	**12**		
	Day	**–28 to –1**	**0**	**30**	**60**	**90**		
Visit Window (in days)		—	—	±7	±7	±7	—	
Concomitant medications and ocular procedures		X[k]	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Note: Except as directed, all ocular assessments should be performed for both eyes.

a. For subjects who discontinue study drug prior to Week 8 (Day 60), perform 30 days (±7 days) following the last injection or study visit.

b. Significant medical/surgical history, including chronic and ongoing conditions (e.g., trauma, cancer history, ophthalmic history). Obtain date of first neovascular AMD diagnosis in the study eye.

c. Perform only at screen, exit and early discontinuation visits

d. Pregnancy test for women of childbearing potential only

e. Haematology will measure haemoglobin, haematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count. Blood chemistry will measure albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, glucose, LDH, inorganic phosphorus, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid will be measured. If the total bilirubin concentration is increased 1.5 times above the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. Urinalysis includes a semi-quantitative "dipstick" evaluation where the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood. If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent by the laboratory for microscopic analysis of WBC, RBC and casts.

f. Perform pre-injection.

g. Perform prior to dilating eyes.

h. Perform on both eyes; the measurement method used for a subject must remain consistent throughout the study

i. Perform pre-injection and 30 minutes (±10 minutes) post-injection in both eyes

j. Injecting physician to perform within 15 minutes post-injection for study eye only

k. Record any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes) and pre- and post-injection medications used within 7 days prior to randomization.

l. In case the investigator is unable to administer the injection on the day of the assessment for some reason, the injection may be administered within +1 to +3 days (considered the same visit), following the assessment.

m. Subjects who discontinue study treatment will continue to be followed-up to undergo safety and ocular procedures every month as per their regularly scheduled visits until study exit.

19 APPENDIX 2. SUMMARY OF CHANGES

Section Changed	Previous language (changed from)	Modified language (changed to)	Reason for change	Impact on subjects (Risk/Benefit)
Amendment 1				
14 Statistical Methods and Considerations	n/a	14.1 Primary Estimand Description added	To add primary estimand per FDA request	None