Clinical Research Protocol ONS-5010-002

TITLE: A CLINICAL EFFECTIVENESS, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF ONS-5010 IN SUBJECTS WITH SUBFOVEAL CHOROIDAL NEOVASCULARIZATION (CNV) SECONDARY TO AGE-RELATED MACULAR DEGENERATION (AMD)

Protocol Number:	ONS-5010-002
Version Date:	V6.0 20 DEC 2019
NCT Number:	NCT03834753
Investigational Product:	ONS-5010 (recombinant humanized anti–human VEGF monoclonal antibody)
Development Phase:	Clinical Effectiveness Study (Phase 3)
Sponsor:	Outlook Therapeutics, Inc.
Lead Principal Investigator:	To be appointed before the end of the study
Medical Monitor:	Name: Dr. Geoffrey Broadhead Telephone: 214 736 3225 E-mail: geoff.broadhead@greenlightclinical.com

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12/19/2019

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Terry J. Dagnon

12/19/2019

Sponsor Signature Terry J Dagnon, MS Chief Operating Officer *Date*

Signer Name: Terry J Dagnon
Signing Reason: I approve this document
Signing Time: 12/19/2019 | 9:07:39 AM PST
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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-5010-002

Protocol Title: **A Clinical Effectiveness, Multicenter, Randomized, Double-masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects with Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (AMD)**

Investigator Signature	*Date*

Print Name and Title

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AMENDMENTS

Amendment Number	Version Number	Date
Amendment 1	v2.0	31 January 2019
Amendment 2	v3.0	21 May 2019
Amendment 3	v4.0	22 August 2019
Amendment 4	v5.0	10 September 2019
Amendment 5	V6.0	20 December 2019

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
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

PROTOCOL SYNOPSIS

TITLE	A clinical effectiveness, multicenter, randomized, double-masked, controlled study of the efficacy and safety of ONS-5010 in subjects with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).
SPONSOR	Outlook Therapeutics, Inc.
NUMBER OF SITES	Approximately 50
RATIONALE	This study will assess the efficacy and safety of intravitreal injections of ONS-5010 (an ophthalmic specific bevacizumab) administered monthly compared with ranibizumab 0.5 mg injections administered for 3 doses and then quarterly in subjects with primary CNV with or without a classic CNV component secondary to age-related macular degeneration (AMD).
STUDY DESIGN	This is a clinical effectiveness, multicenter, randomized, double-masked, controlled study of the efficacy and safety of intravitreally administered ONS-5010. Eligible subjects will be randomized in a 1:1 ratio to receive ONS-5010 or 0.5 mg ranibizumab injections. Subjects randomized to receive ONS-5010 will receive 1.25 mg ONS-5010 by intravitreal injection every month until Day 330. Subjects randomized to receive ranibizumab 0.5 mg injections will be injected with 3 doses (randomization, Day 30, and Day 60) followed by 2 further doses every 90 days (Day 150 & Day 240). Subjects in the ranibizumab group will undergo sham procedures beginning at Day 90 until Day 300, at visits when they do not receive an active ranibizumab injection. There will 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. 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. Only one eye will be chosen as the "study eye." Only the study eye will receive intravitreal injections of ONS-5010 or ranibizumab injection.

PRIMARY OBJECTIVE	The primary 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 difference in proportion of subjects who gain ≥15 letters in best correct visual acuity (BCVA) at 11 months • To evaluate the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to 12 months

SECONDARY OBJECTIVES	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 mean change in BCVA from baseline to 11 months
	  • The proportion of subjects who gain ≥5 or ≥10 letters in visual acuity at 11 months compared with baseline
	  • The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline
	  • The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months
	  • The mean change from baseline in visual acuity over time up to 11 months

SAMPLE SIZE	The study is planned to enroll approximately 220 subjects. The sample size (110 per treatment arm) is adequate for this clinical effectiveness study for the treatment with ophthalmic bevacizumab delivered by monthly intravitreal injections versus ranibizumab administered via the FDA approved PIER (Phase IIIb, 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) dosing regimen. This sample size is based on the primary endpoint of the proportion of subjects who gain ≥15 letters in visual acuity at 11 months, with a treatment effect for the difference in proportions between ONS-5010 (p=0.32) and ranibizumab (p=0.14) of 0.18. The power was set to 90%, using a one-sided α=0.025.
SUBJECT SELECTION	**Inclusion Criteria** All subjects must meet the following criteria to be eligible for study

CRITERIA	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 1. 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 25 to 67 letters read (approximately equivalent to 20/50 to 20/320 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 • Require medical or surgical intervention during the 12-month 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 12-month 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. Pregnant or nursing female patients or females intending to become pregnant within the next 24 months. Patients must have a negative serum pregnancy test within 28 days of the first dose of study treatment in premenopausal women and women < 2 years after the onset of menopause
26. Premenopausal women not using adequate contraception

Adequate contraception methods include:

27. 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
28. 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
29. 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.
30. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)
31. 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
32. 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 6 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. 33. 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 34. Current treatment for active systemic infection **Other** 35. Known allergy to any component of the study drug or history of allergy to fluorescein, not amenable to treatment 36. Inability to obtain fundus photographs, OCT, or fluorescein angiograms of sufficient quality to be analyzed and graded by the Investigator 37. 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 Sham procedure

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	• Subjects randomized to ranibizumab will receive 0.5 mg ranibizumab by intravitreal injection every month for 3 doses (randomization, Day 30 and Day 60) followed by doses every 90 days until day 240. • Subjects randomized to ONS-5010 will receive 1.25 mg of investigational product every month for 12 months. There will be no modification of study drug dose during this study. • Subjects in the ranibizumab group will undergo sham procedures beginning at Day 90 until Day 300, at visits when they do not receive an active ranibizumab injection. • The study concludes at Day 330 in the ranibizumab arm and Day 365 in the ONS-5010 arm. • The efficacy evaluation period will be 11 months for both study arms • The safety evaluation period will be 11 months for the ranibizumab arm and 12 months in the ONS-5010 arm.
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. Protocol specific medications used by a subject during the study are not considered concomitant medications. Also, no other AMD and anti-VEGF treatments other than ONS-5010 or ranibizumab (as randomized) are permitted in the study eye. **Prohibited Treatments in the Study Eye while on Study Treatment:** • Ranibizumab (Lucentis®) – other than protocol specified treatments • Bevacizumab (Avastin®) – other than protocol specified treatments • Aflibercept (Eylea®) • Verteporfin (Visudyne®) • Pegaptanib sodium (Macugen®) • Laser treatment for AMD **Rescue Therapy:** While there is not a prescribed rescue therapy in the protocol, it will be up to the Investigator to determine if a subject should be withdrawn from study treatment due to vision loss (not retinal edema) resulting in a lack of efficacy and to provid rescue therapy. Participants who are discontinued from study treatment due to BCVA decreasing ≥15 letters (3 lines) compared to the baseline BCVA at any visit must receive rescue therapy per the investigator. Every attempt should be made to have subjects continue in the study for safety evaluations, even if subjects are discontinued from study treatment.

PRIMARY EFFICACY ENDPOINT	• The primary efficacy endpoint is the proportion of subjects who gain ≥15 letters in the BCVA score at 11 months compared with baseline
SECONDARY EFFICACY ENDPOINTS	The secondary endpoints are the following: • The mean change in ETDRS BCVA letters read from baseline to 11 months. • The proportion of subjects who gain ≥5 letters in the BCVA score at 11 months compared with baseline • The proportion of subjects who gain ≥10 letters in the BCVA score at 11 months compared with baseline • The proportion of subjects who lose fewer than 15 letters in the BCVA score at 11 months compared with baseline • The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months (legal blindness is defined as both eyes with 20/200 or worse)
EXPLORATORY ENDPOINT	• Mean Absolute Change from Baseline in Central Foveal Thickness at 11 months
SAFETY ENDPOINT	All subjects in the ONS-5010 arm will be followed through Month 12 to assess safety (with masked assessment through Month 11). All subjects in the ranibizumab arm will be followed through Month 11. 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 • The incidence of positive serum antibodies to ONS-5010
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. • 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.

1 BACKGROUND

1.1 Epidemiology of AMD

Age related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the United States, Europe and Australia (Kawasaki et al., 2010, Rein et al., 2009, Smith et al., 2001). More than 1.75 million people in the US currently have one or both eyes affected by the advanced stage of AMD and it is estimated that there are another 7 million individuals "at risk" (Friedman et al., 2004). In Australia, vision loss from AMD is attributed as the main cause of vision loss in 11.1% of non-indigenous Australians (Keel et al., 2017).

Once advanced AMD occurs in one eye, the risk for developing advanced AMD in the second eye over a 5 year period is 43% (Age-Related Eye Disease Study Research, 2001) and the impact is substantial; with AMD accounting for 8.7% of all blindness worldwide (Wong et al., 2014).

These numbers are expected to rise as life expectancies across the Western world continue to increase, where by 2056 in Australia, it is estimated that there will be 8.7 million Australians over the age of 65 (22% of the population) (AIHW, 2017).

1.2 Clinical Features of AMD

AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form (Ferris et al., 1984, Lim et al., 2012, Miller, 2013). Neovascular, or "wet" AMD is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or subretinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (Ferris et al., 1984).

These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss (Shah and Del Priore, 2007, Shah and Del Priore, 2009). Without treatment most affected eyes will have poor central vision (20/200) within 12 months (Blinder et al., 2003). Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments (Ferris, 1983, Sommer et al., 1991, Wong et al., 2008).

1.3 Vascular Endothelial Growth Factor (VEGF)

VEGF has been shown to be elevated in patients with neovascular AMD and is thought to play a key role in the neovascularization process (Spilsbury et al., 2000). The use of intravitreal (IVT) pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with neovascular AMD (Bloch et al., 2012, Campbell et al., 2012). Anti-VEGF treatments, such as ranibizumab (Lucentis®), aflibercept (Eylea®) and bevacizumab (Avastin®) inhibit VEGF signaling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal edema (Al-Latayfeh et al., 2012).

1.4 Anti-VEGF treatments for wet AMD

While VEGF inhibitors have vastly improved patient outcomes for wet AMD, the per dose costs for the therapies licensed specifically for use in the eye (Lucentis® and Eylea®) remains extremely high compared to the equivalent per-dose cost for Avastin® in several jurisdictions.

One of the many factors that contribute to selection of a drug for a patient is cost. A single dose of ranibizumab costs 40 times as much as a single dose of bevacizumab (per-dose cost, approximately $2,000 for ranibizumab and $50 for bevacizumab). This cost differential has important economic implications when extrapolated to the more than 250,000 patients who are treated for neovascular AMD annually in the United States (Group et al., 2011).

Lucentis® was approved for treatment of wet AMD by the US FDA in 2006. Avastin® was initially approved for the treatment of colorectal cancer in 2004, with the approved indications expanding to include several other cancers following the initial approval. While Avastin® has been used by ophthalmologists extensively for the past 14 years for the treatment of wet AMD, use in this indication remains off-label in most jurisdictions (Grisanti and Ziemssen, 2007).

1.5 Ranibizumab (Lucentis®)

Ranibizumab (Lucentis®) is a humanized recombinant monoclonal antibody fragment targeted against human VEGF. It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularization, as well as vascular leakage, which contribute to the progression of wet AMD and development of choroidal neovascularization (CNV), and macular edema causing visual impairment in diabetes and retinal vein occlusion.

1.6 Bevacizumab (Avastin®, ONS-5010)

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody (93% human, 7% murine sequences - molecular weight 149 kDa) that selectively binds with high affinity to all isoforms of human VEGF and neutralizes VEGF's biological activity through a steric blocking of the binding of VEGF to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells. Receptor activation normally induces tyrosine phosphorylation and a subsequent series of signal transduction events that elicits mitogenic and pro-survival activity signals for the vascular endothelial cells.

Since there is a very low or undetectable expression of VEGF receptors in most normal tissues (with exception of renal glomeruli) but a significant up-regulation in the vasculature of many tumors (including colorectal cancer), the neutralization of VEGF by bevacizumab provides a relative specific inhibition of the tumor angiogenesis thereby inhibiting tumor growth and metastases.

Injected intravitreally, bevacizumab promotes marked regression of intraocular neovascularization in clinical studies of neovascularizing ocular disease (Avery et al., 2006, Rich et al., 2006, Yoganathan et al., 2006). Further, bevacizumab has been demonstrated to

have positive clinical effects in the management of DME, as reviewed by Yilmaz et.al (Yilmaz et al., 2011).

Bevacizumab has been demonstrated to be as effective as ranibizumab in the treatment of AMD and DME, however it is not licensed for use in the indication in any jurisdiction, and as such, intraocular use of bevacizumab remains off label.

The current study will utilize ONS-5010 (the drug product - a recombinant humanized anti–human VEGF monoclonal antibody specialized for ophthalmic use), which contains ONS-1045 (bevacizumab) as the active drug substance.

1.7 Bevacizumab and ranibizumab in clinical use

The Comparison of AMD Treatments Trials (CATT) study compared the relative safety and effectiveness of Lucentis® and Avastin® in a multicenter clinical trial, which determined that both treatments are equally effective in improving vision when administered monthly or on an as-needed basis (Group et al., 2011).

However, the use of Avastin® off-label in the treatment of neovascular eye disease requires larger volumes of commercially available Avastin® (usually supplied in 100mg/4mL and 400mg/16mL vials) to be fractionated and repackaged by compounding pharmacies into appropriate volumes for use in "off-label" intravitreal injection.

The compounding process required to fractionate Avastin® into appropriate doses for intravitreal use can potentially pose a significant public health risk, where contamination in the compounding process has been linked to several cases of infectious and non-infectious endophthalmitis (Sheyman et al., 2013, Goldberg et al., 2012).

Further, independent laboratory studies of fractionated Avastin® sourced from 11 separate compounding pharmacies in the United States showed that 81% of samples (17 of 21 individual fractionated doses) had lower protein concentrations (mean [SD], 22.2 [4.9] mg/mL; range, 19.2-24.5 mg/mL) than Avastin® sourced directly from the manufacturer, Genentech (Yannuzzi et al., 2015).

The high cost per-dose for Lucentis®, coupled with the concerns regarding the inter-batch quality of compounded Avastin® and the potential for contamination and subsequent ocular complication with off-label use of Avastin®, has indicated that an ophthalmic specific, appropriately packaged bevacizumab could provide increased access to effective treatment for a wider number of people affected by wet AMD. ONS-5010 is intended to fulfill these requirements.

2 STUDY RATIONALE

This study will assess the efficacy and safety of intravitreal injections of ONS-5010 administered monthly, compared with ranibizumab 0.5 mg injections administered for 3 doses and then quarterly in subjects with primary subfoveal choroidal neovascularization (CNV) with or without a classic CNV component secondary to AMD.

2.1 Risk/Benefit Assessment

The safety and efficacy of intravitreal anti-VEGF therapy for wet AMD has been well established in numerous clinical studies.

The Phase I trial of the drug substance ONS-1045 demonstrated that it is bioequivalent to both US and EU sourced Avastin®. ONS-1045 is the active drug substance in the investigational drug product, ONS-5010 that will be administered in this study.

Both bevacizumab and ranibizumab have been demonstrated to be equivalent in the treatment of wet AMD. The dosing regimen employed in this study will provide participants with treatment equivalent to standard-of-care.

3 STUDY OBJECTIVES

3.1 Primary Objective

This study will assess the efficacy and safety of intravitreal injections of ONS-5010 1.25 mg administered monthly compared with ranibizumab 0.5 mg injections administered as 3 doses and then quarterly in subjects with primary subfoveal choroidal neovascularization (CNV) with or without a classic CNV component secondary to AMD.

The primary objectives of the study are as follows:

1. To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss, as measured by the difference in proportion of subjects who gain ≥15 letters in best corrected visual acuity (BCVA) at 11 months
2. To evaluate the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to 12 months

3.2 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 mean change in BCVA from baseline to 11 months
  - The proportion of subjects who gain ≥5 or ≥10 letters in visual acuity at 11 months compared with baseline
  - The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline
  - The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months

4 STUDY DESIGN

4.1 Study Overview

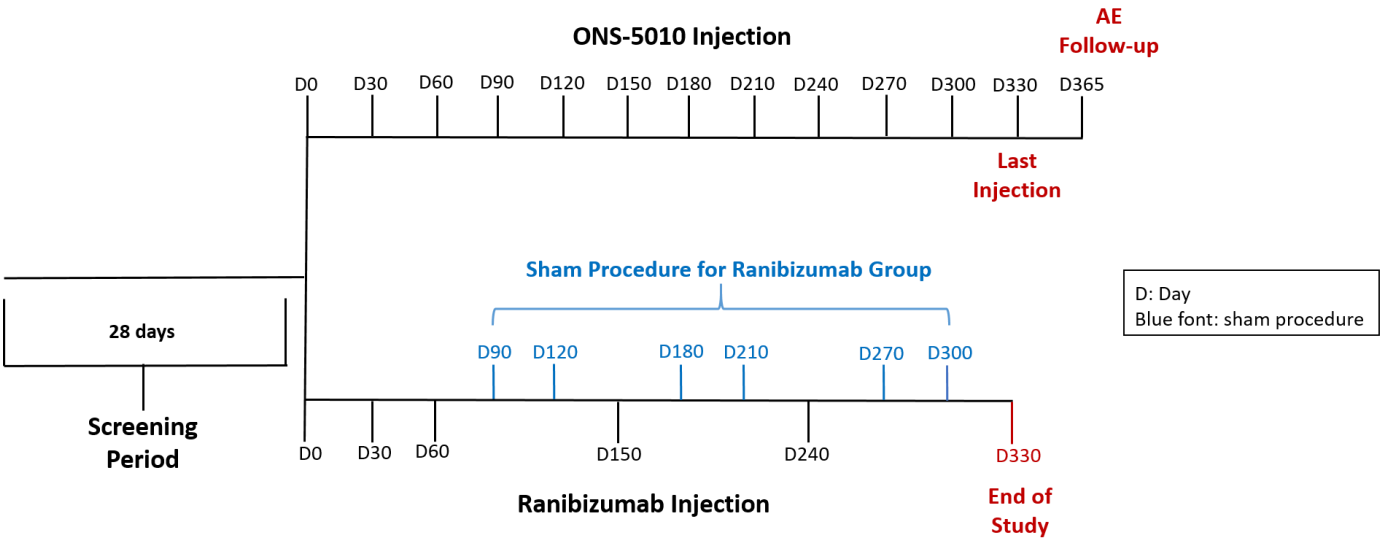
This is a clinical effectiveness, multicenter, randomized, double-masked, controlled study of the efficacy and safety of intravitreally administered ONS-5010. Approximately 220 subjects with

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 50 study sites in the United States.

Eligible subjects will be randomized in a 1:1 ratio to receive 1.25 mg ONS-5010 or 0.5 mg ranibizumab injections via the FDA approved PIER dosing regimen. Subjects randomized to receive ONS-5010 will receive 1.25 mg ONS-5010 by intravitreal injection every month until Day 330. Subjects randomized to receive ranibizumab 0.5 mg injections will be injected at 3 time points (randomization, Day 30, and Day 60) followed by a further 2 doses every 90 Days (Day 150 and Day 240). Subjects in the ranibizumab group will undergo sham procedures beginning at Day 90 until Day 300, at visits when they do not receive an active ranibizumab injection.

There must be a minimum of two investigators per study site to fulfil 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. 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. Only one eye will be chosen as the "study eye." Only the study eye will receive intravitreal injections of ONS-5010 or ranibizumab injection. Subjects will be scheduled for study visits throughout the study.

4.2 Study Design & Injection/Sham Schedule



5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who gain ≥15 letters in the BCVA score at 11 months compared with baseline, 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 mean change in BCVA score from baseline to 11 months, where BCVA is based on the ETDRS visual acuity assessment, to be analyzed as a continuous variable. As an adjunct to this endpoint analysis, the pattern of the mean change from baseline in the BCVA score over successive visits up to 11 months will be statistically evaluated, to assist in understanding how rapidly change may occur.
- The proportion of subjects who gain ≥5 letters in the BCVA score at 11 months compared with baseline
- The proportion of subjects who gain ≥10 letters in the BCVA score at 11 months compared with baseline
- The proportion of subjects who lose fewer than 15 letters in the BCVA score at 11 months compared with baseline
- Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months

5.3 Exploratory Endpoint

Mean Absolute Change from Baseline in Central Foveal Thickness at 11 months

5.4 Safety Endpoints

All subjects in the ONS-5010 arm will be followed through Month 12 to assess safety (with masked assessment through Month 11). All subjects in the ranibizumab arm will be followed through Month 11. 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
- The incidence of positive serum antibodies to ONS-5010

6 PARTICIPANT SELECTION

6.1 Study Population

Approximately 220 subjects (110 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 1. 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 25 to 67 letters read (approximately equivalent to 20/50 to 20/320 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 1: 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 12-month 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 12-month 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. Pregnant or nursing female patients or females intending to become pregnant within the next 24 months. Patients must have a negative serum pregnancy test within 28 days of the first dose of study treatment in premenopausal women and women < 2 years after the onset of menopause
26. Premenopausal women not using adequate contraception.

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 6 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.

27. 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
28. Current treatment for active systemic infection

Other

29. Known allergy to any component of the study drug or history of allergy to fluorescein, not amenable to treatment
30. Inability to obtain fundus photographs, OCT, or fluorescein angiograms of sufficient quality to be analyzed and graded by the Investigator
31. 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®) - other than protocol specified treatments
- Bevacizumab (Avastin®) - other than protocol specified treatments
- Aflibercept (Eylea®)
- Pegaptanib sodium **(**Macugen®)
- Verteporfin (Visudyne®)
- Laser treatment for AMD

7.2 Rescue Therapy

While there is not a prescribed rescue therapy in the protocol, it will be up to the Investigator to determine if a subject should be withdrawn from study treatment due to vision loss (not retinal edema) resulting in a lack of efficacy and to provide rescue therapy. Participants who are

discontinued from study treatment due to BCVA decreasing ≥15 letters (3 lines) compared to the baseline BCVA at any visit must receive rescue therapy per the investigator. Every attempt should be made to have subjects continue in the study for safety evaluations, even if subjects are discontinued from study treatment.

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 ratioto receive either 1.25 mg ONS-5010 or 0.5 mg ranibizumab injections over the study period. Subjects in the ranibizumab group will undergo sham procedures beginning at Day 90 until Day 300, at visits when they do not receive an active ranibizumab injection. Two hundred and twenty (220) subjects are currently planned to be randomized for 190 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 (or sham) 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, unmasked study coordinators, and unmasked clinical research associates (CRA) 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 unblinded 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 slight brown, opalescent liquid.

ONS-5010 will be provided in 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. Instructions for administration will be in the Manual of Procedures. There will be no on-site compounding of the investigational product.

8.3.2 Ranibizumab [Lucentis®] (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 one 2-cc glass vial of study drug, one 5-micron, 19-gauge x 1-1/2-inch filter needle for withdrawal of the vial contents, and one 30-gauge x 1/2-inch injection needle for the intravitreal injection. Vials are for single eye use only.

Sites will use commercially available ranibizumab (Lucentis®) procured regionally 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 every month for 3 doses (randomization, Day 30 and Day 60) followed by doses every 90 days (at Day 150 and Day 240).

Subjects randomized to ONS-5010 will receive 1.25 mg (in 0.05 ml of solution) every month until Day 330. 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. The study concludes at Day 330 for subjects on the ranibizumab arm and Day 365 for subjects on the ONS-5010 arm. Subjects on the ranibizumab arm will revert to Standard of Care upon completion of the Day 330 visit. Subjects randomized to ONS-5010 will revert to Standard of Care upon completion of the Day 365 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 Administration of sham procedure

Beginning at Day 90 and up to Day 300, at visits when subjects do not receive an active ranibizumab injection, a sham procedure will be performed. A minimum of five minutes prior to sham procedure, 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 sham procedure 5% povidone iodine for ophthalmic use is applied to the injection site. For the sham procedure the tip of an injection syringe (the hub without a needle) will be used on the entry site without actually penetrating the eye for an approximate amount of time it would take to perform an IVT injection.

8.7 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. The standardized procedure for post-injection assessment is described in the Manual of Procedures.

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. (See Section 7.2)

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.

8.8 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 monitor will verify these documents throughout the course of the study.

Unused or outdated vials must be returned to the Sponsor 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. Study Procedures are further described in the Manual of Procedures.

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 (for all participants) and day 330 for those participants in the ranibizumab arm (after unmasking) and day 365 for those participants in the ONS-5010 arm or early discontinuation visits. 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 adnexae, 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 performed pre-injection on both eyes at all visits according to the Manual of Procedures. 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 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 autofluorescense and photography will be performed according to the Manual of Procedures.

9.2.8 Fluorescein angiography

Fluorescein angiography will be performed pre-injection on both eyes at screening (Visit 1), days 90, Study Exit visit and early discontinaution visits according to the Manual of Procedures.

Certification of the equipment and examiners for 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.

9.3.5 Serum samples for antibodies to ONS-5010 and measurement of ONS-5010 concentrations

Approximately 5 patients randomized to the ONS-5010 arm will undergo serum sampling for pharmacokinetic (PK) and immunogenicity testing at approximately 2 selected sites. The selection of patients who will take part in the PK and immunogenicity testing will be restricted to those receiving monocular ONS-5010 treatment **in the study eye only**, with no anti-VEGF treatment **of any kind** in the fellow eye. Serum samples for analysis of antibodies to ONS-5010, and ONS-5010 concentration measurement will be collected pre-dose at Day 0, Day 1, Day 2, Day 3 and Day 4. Further serum samples for analysis of antibodies to ONS-5010 will be collected pre-dose at Day 30, Day 31, Day 32, Day 33, Day 34 and Day 240. Masking will be maintained by informing all subjects that they may be randomly selected for serum sampling.

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
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 is 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 is any

10.4 Visit 4 (Day 60±7)

1. Record concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Collect blood for clinical laboratory tests
4. Collect urine for clinical laboratory tests
5. Perform BCVA in both eyes
6. Perform IOP pre-injection and before dilation in both eyes

7. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
8. Perform OCT examination in both eyes
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 if injection is given
11. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes if injection is given
12. Record adverse events if there is any

10.5 Visit 5 (Day 90±7)

1. Record 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 fundus autofluorescence & fundus photography
8. Perform fluorescein angiography
9. Perform injection of ONS-5010 or sham procedure 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 if injection is given
11. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes if injection is given
12. Record adverse events if there is any

10.6 Visit 6 (Day 120±7)

1. Record 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 sham procedure 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 if injection is given
9. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes if injection is given

10. Record adverse events if there is any

10.7 Visit 7 (Day 150±7)

1. Record concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Collect blood for clinical laboratory tests
4. Collect urine for clinical laboratory tests
5. Perform BCVA in both eyes
6. Perform IOP pre-injection and before dilation in both eyes
7. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
8. Perform OCT examination in both eyes
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 if injection is given
11. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes if injection is given
12. Record adverse events if there is any

10.8 Visit 8 (Day 180±7)

1. Record 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 sham procedure 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 if injection is given
9. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes if injection is given
10. Record adverse events if there is any

10.9 Visit 9 (Day 210±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 sham procedure 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 is any

10.10 Visit 10 (Day 240±7)

1. Record concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Collect blood for clinical laboratory tests
4. Collect urine for clinical laboratory tests
5. Perform BCVA in both eyes
6. Perform IOP pre-injection and before dilation in both eyes
7. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
8. Perform OCT examination in both eyes
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 if injection is given
11. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes if injection is given
12. Record adverse events if there is any

10.11 Visit 11 (Day 270±7)

1. Record 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 sham procedure 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 if injection is given

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

10.12 Visit 12 (Day 300±7)

1. Record 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 for those subjects on the ONS-5010 arm
5. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes for all participants
6. Perform OCT examination in both eyes for all participants
7. Perform injection of ONS-5010 or sham procedure in the study eye only
8. Injecting physician to perform finger count, hand motion, light perception within 15 minutes post-injection for study eye
9. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes
10. Record adverse events if there is any for all participants

10.13 Visit 13 (Day 330±7)

1. Record concomitant medication use and concurrent ocular procedures
2. Perform and record vital signs
3. Perform a review of body systems in ranibizumab arm only
4. Collect blood for clinical laboratory tests in ranibizumab arm only
5. Collect urine for clinical laboratory tests in ranibizumab arm only
6. Perform BCVA in both eyes
7. Perform IOP before dilation in both eyes for subjects in ranibizumab arm and pre-injection only in ONS-5010 arm
8. Perform the slit lamp exam and dilated ophthalmoscopy in both eyes
9. Perform OCT examination in both eyes
10. Perform fundus autofluorescence and fundus photography
11. Perform fluorescein angiography
12. Unmask participant and Investigator; ranibizumab arm subjects will revert to Standard of Care and exit the study
13. Perform serum pregnancy test for women of childbearing potential for ranibizumab arm participants only

14. Perform injection of ONS-5010 in the study eye only to those participants in the ONS-5010 arm.
15. Injecting physician to perform finger count, hand motion, light perception within 15 minutes post-injection for study eye only to those participants in the ONS-5010 arm
16. Perform IOP 30 minutes (±10 minutes) post-injection in both eyes to those participants in the ONS-5010 arm.
17. Record adverse events if there is any

10.14 Visit 14 (Day 365±7) (for participants in ONS-5010 arm only)/ Early termination visit

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 for subjects who withdraw prior to Month 12 at selected sites
11. Perform fundus autofluorescence & fundus photography
12. Perform fluorescein angiography
13. Record adverse events if there is any

10.15 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 for subjects who withdraw prior to Month 12 at selected sites
11. Perform fundus autofluorescence & fundus photography
12. Perform fluorescein angiography
13. Record adverse events if there is any

10.16 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 day 330.

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 is any

10.17 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 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 or of greater severity or frequency than expected based on the information in the 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, for 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

The relationship of an AE to the investigational product or procedure should be assessed using the following guidelines in Table 2.

Table 2. AE Relationship to Investigational Product or Procedure

Relationship	Comment
Definitely	Previously known toxicity of investigational product or known complication of procedure; or an event that follows a reasonable temporal sequence from administration of the investigational product or procedure; that follows a known or expected response pattern to the suspected investigational product or procedure; if suspected investigational product is confirmed by stopping or reducing the dosage of the investigational product; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the investigational product or procedure; that follows a known or expected response pattern to the investigational product or procedure; if suspected investigational product is confirmed by stopping or reducing the dosage of the investigational product; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the investigational product or procedure; that follows a known or expected response pattern to that investigational product or procedure; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the investigational product or procedure.

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 events
- 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 via the EDC system to Green Light Clinical Pharmacovigilance, 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 ONS5010_safety@greenlightclinical.com, within 24 hours of the first awareness of the event.

11.3 Medical Monitoring

The Medical Monitor for this study should be contacted directly at the number below to report medical concerns or questions regarding safety.

Name: Dr. Geoffrey Broadhead
Telephone: +61 2 8091 3699
+1 214 736 3225
E-mail: geoff.broadhead@greenlightclinical.com

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 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 will result 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 Efficacy Analysis

The ITT population is defined as all subjects who are randomized. All efficacy data will be presented by randomized treatment group, and all efficacy analyses will be performed on the ITT population for the primary analysis. The analysis for efficacy endpoints will also be performed on the PP population.

Subjects who discontinue study treatment and do not receive any rescue/prohibited therapy, and are willing to remain in the study, will be followed and evaluated for efficacy through the end of study. These subjects will be included in the analysis of the primary and secondary efficacy endpoints.

Subjects who discontinue study treatment and receive rescue/prohibited therapy or discontinued from study due to lack-of-efficacy or adverse event, will be included in analyses for the primary efficacy endpoint (and similar secondary endpoints) as a non-responder, and will be treated as described below for the applicable mean change from baseline secondary efficacy endpoint.

The primary efficacy analysis will employ a Fisher's Exact test to assess a significant difference in the proportion of subjects who gain ≥15 letters in visual acuity between ONS-5010 and Ranibizumab. The difference in proportions and it's 95% confidence interval will be reported.

A Trimmed Means statistical approach as described by Permutt and Li will be used for the first secondary efficacy analysis. Two methods of trimming will be used, a fixed approach and an adaptive approach. The fixed method will be treated as the first secondary analysis method, and the adaptive method shall be considered the second secondary analysis method. The fixed approach is selected as the first secondary analysis due to its ease of interpretability, i.e. a

comparison of the better halves of each group. If the dropout rate in either treatment group is greater than the planned trimmed fraction in the fixed approach, the adaptive approach will be considered the first secondary, as suggested by Permutt and Li.

- Using an analysis of covariance (ANCOVA), a linear model is fit to the data with treatment and baseline BCVA score as covariates. The beta coefficient for treatment is discarded and only the Y (outcome), the beta coefficient for baseline score, and X (baseline score) are considered. $Y - \beta(X)$ is then calculated for each subject for the purpose of ranking.

- For the fixed approach, the best 50% (subjects with $Y - \beta(X)$ observations better than the median $Y - \beta(X)$ observation) of observations in both the active and control group will be subset. For the calculation of the median, dropouts will be included as observations worse than the median.

- For the adaptive approach, first the proportion of subjects who dropped out of the control and treatment arms are identified. This greater proportion of the two arms is then used as the percentile floor in which observations must be better. Those observations that are not better than the floor are trimmed (removed). Dropouts are again included in the calculation of the percentile floor value as values worse than the percentile.

- After trimming is done, an ANCOVA is used again on the two analysis sets to find an observed treatment effect. To determine the p-value and 95% CI, 10,000 permutations of the data will be run and the trimming methodology will be repeated. The number of permutations that result in an effect size greater than the observed effect size divided by the number of permutations will be the p-value. The 95% CI will be calculated using the 2.5 and 97.5 percentiles of the permutation distribution. A permutation dataset will be outputted using the Proc Multtest procedure in SAS, using seed: 7416 for the fixed approach, and 4384 for the adaptive approach. For PP population analyses the seeds will be 2131 and 4904, respectively. Seeds were generated using random.org.

As complements to the first secondaryefficacy analysis, the following statistical methods will be used:

- The first complementary analysis will be performed using an ANCOVA model with treatment group as a fixed effect and the baseline BCVA as a continuous covariate.

- The second complementary analysis will employ the multiple imputation method that will replace each missing 11-month BCVA value with a set of plausible values that represents the uncertainty of the correct value based on the observed time matched data at all other visits. These multiple imputed datasets are then analyzed by using standard procedures for complete data and then combining the results from these analyses. The multiple imputation will be completed by two steps (1) imputing these intermittent missing data using Markov chain Monte Carlo (MCMC) methods to get a monotone missingness data pattern; (2) then

using regression method to impute 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 makes the assumption that missing data are missing at random (MAR), a sensitivity analysis will be performed to assess if MAR is a reasonable assumption.

- The third complementary analysis will be performed on BCVA over time, using repeated measures, mixed model methodology. 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. In addition, a descriptive summary of mean change from baseline over time will be tabulated by visit and treatment group and presented in a figure.

The remaining secondary analyses will be performed, using Fisher's Exact test for the significance of differences between the ONS-5010 and the 0.5 mg ranibizumab dose group. Given that the primary efficacy analysis and the first secondary efficacy analysis are significant, a hierarchical testing method will be used to control Type 1 error at an overall two-sided 0.05 level. The difference in proportions will be presented along with their respective 95% CIs. The significance testing for secondary endpoints will be conducted in the order listed below, where each successive endpoint analysis will be considered statistically significant only if the prior analysis in the hierarchy is statistically significant..

- The proportion of subjects who gain ≥5 letters in the BCVA score at 11 months compared with baseline
- The proportion of subjects who gain ≥10 letters in the BCVA score at 11 months compared with baseline
- The proportion of subjects who lose fewer than 15 letters in the BCVA score at 11 months compared with baseline
- Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months

Subjects who discontinue for AE, lack-of-efficacy, or rescue therapy will be categorized as non-responders. Subjects who discontinue for other reasons and have a missing 11 month BCVA score will be treated as missing.

14.2 Control of Type 1 error

A fixed-sequence hierarchical method for Type 1 error control will be used for efficacy analyses for the difference between ONS-5010 and ranibizumab. Following a statistically significant result for the primary endpoint, the secondary endpoints will be analyzed in the

order specified, with each analysis conducted at the two-sided 0.05 level. The conclusion for statistical significance of any endpoint will only be made if all prior endpoints were statistically significant. This method guarantees control of Type 1 error.

14.3 Pooled Efficacy Analysis

Protocols ONS-5010-001 (001) and ONS-5010-002 (002) are similar study designs.

A pooled efficacy analysis of subjects in protocols 001 and 002 will be conducted to assess more precise estimates of efficacy, with a smaller confidence interval. The pooled efficacy analysis will be governed by a separate Statistical Analysis Plan.

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.

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, prior and concomitant medications. The collected partial dates will be reported in the listings.

Missing efficacy data will be explored to identify any missing data patterns and mechanisms. The methods for dealing with missing data will be reviewed and may be refined during blinded review of the data (ICH-E9). Particular attention will be paid to the reasons for discontinuation and to determine if there are differences between the treatment groups for missing efficacy data, such as an increased frequency of discontinuation for lack of efficacy or adverse event.

A Trimmed Means statistical approach will be used as the first secondary efficacy analysis. This analysis will follow the methodology laid out in Permutt and Li, 2017.

For subjects who have a missing BCVA at the primary efficacy timepoint of 11 months, a multiple imputation method will be used to support the first secondary efficacy analysis. Missing BCVA data will have values imputed using a multiple 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 first secondary efficacy analysis, including analysis of the last observation carried forward (LOCF), jump to reference and a completer

analysis. These analyses will be interpreted in relation to the patterns of missing data and/or reasons for discontinuations. Complete details for these analyses are included in the statistical analysis plan.

14.5 Determination of Sample Size

A sample size of 220 participants (110 per treatment arm) is adequate for this Phase 3 clinical evidence study for the treatment with ophthalmic bevacizumab delivered by monthly intravitreal injections versus ranibizumab administered via the FDA approved PIER dosing regimen. This sample size is based on the primary endpoint of the proportion of subjects who gain ≥15 letters in visual acuity at 11 months, with a treatment effect for the difference in proportions between ONS-5010 (p=0.32) and ranibizumab (p=0.14) of 0.18. The power was set to 90%, using a one-sided α=0.025.

14.6 Demographic and Baseline Characteristics

Participant demographic and baseline variables (age, sex, ethnicity, race, height, weight, and BMI) will be summarised with descriptive statistics. Sex, ethnicity, and race will be summarised with frequency counts and percentages. Baseline ocular assessments will be summarised descriptively as well.

Pregnancy test results, concomitant medication and medical history data for each participant will be presented in data listings and summarised 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 have 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. A safety review will be conducted by a board certified retina specialist at the request of the Medical Monitor.

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-5010-002	Treatment Phase														Early Discontinuation[a]	Follow-up visit[p]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Day	–28 to –1	0	30	60	90	120	150	180	210	240	270	300	330[l]	365[m]		
Visit Window (in days)	—	—	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	—	
Informed consent	X															
Inclusion/exclusion criteria	X															
Medical and surgical history[b]	X															
Demographic data	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height and Weight	X															
Review of body systemsf[c]	X												X[n]	X	X	
Serum pregnancy test[d]	X												X[n]	X	X	
Laboratory samples (haematology, chemistries, urinalysis)[e,f]	X			X			X			X			X[n]	X	X	
Best corrected visual acuity (4-meter test distance)[f, g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination & lens grading[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intraocular pressure[h]	X	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[q]	X	X	X
Dilated ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fundus photography[f]	X				X								X	X	X	

ONS-5010-002	Treatment Phase														Early Discontinuation[a]	Follow-up visit[p]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Day	–28 to –1	0	30	60	90	120	150	180	210	240	270	300	330[l]	365[m]		
Visit Window (in days)	—	—	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	—	
Fundus autofluorescence[f]	X				X								X	X	X	
Fluorescein angiography[f]	X				X								X	X	X	
OCT[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
-Treatment Group- **Study Drug (ONS-5010) Administration[o]**		X	X	X	X	X	X	X	X	X	X	X	X			
-Control Group- **Ranibizumab Administration[o]**		X	X	X			X			X						
-Control Group- **Sham procedure[o]**					X	X		X	X		X	X				
Finger count, hand motion, light perception (if indicated)[j]		X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medications	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent ocular procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	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 Day 330, 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. For women of childbearing potential.
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. 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. At Day 330 – Subjects on the ranibizumab arm will exit the trial and revert to standard of care
m. Visit 14 at Day 365 for subjects in the ONS-5010 arm only or early termination visit for subjects who are withdrawn from the study
n. For those subjects in the ranibizumab arm only (at day 330 after unmasking)
o. 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.
p. 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 termination.
q. Perform IOP measurement for subjects in ranibizumab arm (no injection given) and perform pre-injection and post-injection for subjects in ONS-5010 arm.

19 APPENDIX 2. SUMMARY OF CHANGES FOR AMENDMENTS

Section Changed	Previous language (changed from)	Modified language (changed to)	Reason for change	Impact on subjects (Risk/Benefit)
Amendment 5				
3.1 Primary Objective	To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss, as measured by the mean change in best corrected visual acuity (BCVA) from baseline to 11 months	To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss, as measured by the difference in proportion of subjects who gain ≥15 letters in best corrected visual acuity (BCVA) at 11 months	To better demonstrate the difference in efficacy between study arms	None

3.2 Secondary Objectives	• 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 gain ≥5, ≥10, or ≥15 letters in visual acuity at 11 months compared with baseline
	  • The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline
	  • The mean change from baseline in visual acuity over time up to 11 months
	  • The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months
		• To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss as measured by the following:
		  • The mean change in BCVA from baseline to 11 months
		  • The proportion of subjects who gain ≥5 or ≥10 letters in visual acuity at 11 months compared with baseline
		  • The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline
		  • The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months
			To adjust for the new primary objective	None

5.1 Primary efficacy endpoint	The primary efficacy endpoint is the mean change in BCVA score from baseline to 11 months, where BCVA is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity assessment, to be analyzed as a continuous variable. As an adjunct to the primary endpoint analysis, the pattern of the mean change from baseline in the BCVA score over successive visits up to 11 months will be statistically evaluated, to assist in understanding how rapidly change may occur.	The primary efficacy endpoint is the proportion of subjects who gain ≥15 letters in the BCVA score at 11 months compared with baseline, where BCVA is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity assessment.	To match the primary objective	None

5.2 Secondary efficacy endpoints	The secondary endpoints include the following, all to be analyzed as categorical data:
	  • The proportion of subjects who gain ≥5 letters in the BCVA score at 11 months compared with baseline
		The secondary endpoints include the following:
		  • The mean change in BCVA score from baseline to 11 months, where BCVA is based on the ETDRS visual acuity assessment, to be analyzed as a continuous variable. As an adjunct to this endpoint analysis, the pattern of the mean change from
			To match the secondary objective	None

	• The proportion of subjects who gain ≥10 letters in the BCVA score at 11 months compared with baseline • The proportion of subjects who gain ≥15 letters in the BCVA score at 11 months compared with baseline • Mean change from baseline in the BCVA score over time up to 11 months • The proportion of subjects who lose fewer than 15 letters in the BCVA score at 11 months compared with baseline • Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months	baseline in the BCVA score over successive visits up to 11 months will be statistically evaluated, to assist in understanding how rapidly change may occur. • The proportion of subjects who gain ≥5 letters in the BCVA score at 11 months compared with baseline • The proportion of subjects who gain ≥10 letters in the BCVA score at 11 months compared with baseline • The proportion of subjects who lose fewer than 15 letters in the BCVA score at 11 months compared with baseline • Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months		
6.2 Inclusion Criteria	5. Study eye must:	5. As confirmed by the Investigator and independent image reviewer, the sStudy eye must:	To clarify that these criteria must be confirmed by both the Investigator and the independent image reviewer	None
6.3 Exclusion Criteria	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 cannot exceed –8 diopters of myopia	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	To clarify documentation for high myopia in post cataract surgery patients	None
9.2.8 FA and ICG and throughout the protocol where ICG is described	Indocyanine green angiography will be performed pre-injection on both eyes at screening (Visit 1) according to the Manual of Procedures, to exclude PCV.	(removed)	PCV is less likely in the US population and can be assessed on FA	Decrease risk of allergic reaction to ICG dye
9.3.5 Serum samples for antibodies to ONS-5010 and measurement of ONS-5010 concentrations		Added timepoint: Day 240	To assess full PK course	One additional blood draw for subjects participating in PK sampling
Section 10 and Appendix 1	Fundus photographs collected at Visits 6 – 12	Remove collection of fundus photographs at Visits 6 – 12	These assessments were not contributing to a study endpoint	None
14 Statistical methods and considerations		Adjusted throughout to match the changes above in primary and secondary objectives, endpoints and sample size	To align objectives and endpoings	None

Throughout the protocol		Administrative edits	For clarity and consistency	None
Amendment 4				
Throughout the protocol, description of the population	primary or recurrent subfoveal choroidal neovascularization (CNV) with or without a classic CNV component secondary to AMD	primary subfoveal choroidal neovascularization (CNV) with or without a classic CNV component secondary to AMD	The study population is being simplified to primary lesions only	None
3.2 Secondary Objectives	• The proportion of subjects who gain ≥15 letters in visual acuity at 11 months compared with baseline • The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline	• The proportion of subjects who gain ≥5, ≥10, or ≥15 letters in visual acuity at 11 months compared with baseline • The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline • The mean change from baseline in visual acuity over time up to 11 months	To bring into alignment with the secondary endpoints	None
6.0 Participant Selection	Subjects may be re-screened once where there was a screen fail due to an inactive lesion. Re-screening may occur if necessary, approximately 1 month after the screening visit. Assessments should be repeated at the discretion of the Investigator to determine if the inactive lesion has become active and should include at least BCVA and OCT. Naïve treatment prior treatment patients and patients receiving bilateral anti-VEGF treatment for AMD are eligible. If patients with prior anti-VEGF treatment **in the study eye** are enrolled, a wash out period of 6 weeks from the last injection **in the study eye** to randomization is required in order to be eligible. Patients receiving anti-VEGF treatment in the **fellow eye** at the time of enrolment will **not** be required to undertake a 6 week wash out period **for the fellow eye** prior to randomization. Recurrent: Previously diagnosed and regressed but currently presenting with a new, active component (previous anti-VEGF therapy) is allowed so long as there is at least a 6 week wash out period from the last injection to randomization and there remains active leakage on FA	Text deleted	text is not necessary given the simplification to primary lesions only	None
6.2 Inclusion Criteria	• Be free of scarring within 2 disc diameters of the fovea • Be free of atrophy within 2 disc diameters of the fovea	• Be free of scarring, fibrosis, or atrophy involving the central foveal zone (inner most ring on OCT)	To to clarify distance to the fovea for scarring, fibrosis and atrophy	None

7.0 Concomitant Medications	Should the fellow eye require treatment during the study with an anti-VEGF, a drug which is approved for the treatment of exudative AMD in the respective country should be applied at the discretion of the Investigator and following the procedures established at the respective site.	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.	To clarify fellow eye treatments are at the investigator's discretion	None
7.2 Rescue Therapy	Participants who are discontinued from study treatment due to BCVA decreasing ≥15 letters (3 lines) compared to the baseline BCVA at any visit may receive rescue therapy per the investigator.	Participants who are discontinued from study treatment due to BCVA decreasing ≥15 letters (3 lines) compared to the baseline BCVA at any visit must receive rescue therapy per the investigator.	To clarify rescue therapy should be	Decrease risk of clinically significant loss of vision
14.3 Pooled Efficacy Analysis	A pooled efficacy analysis of subjects in protocols 001 and 002 will be conducted to assess a more precise estimate of efficacy, with a smaller confidence interval. Based on a two-sided 95% confidence level and a standard deviation of 15 letters, the expected precisions (distance from mean difference to limits) for 001 and 002 are 8.53 and 4.84, respectively. The pooled analysis has an expected precision of 4.18. All efficacy analyses previously described in Section 14.1, will be repeated for this pooled analysis. For the ITT population fixed and adaptive trimmed means analyses the seeds to be used will be 6836 and 5897, respectively. For the PP population analyses, the seeds to be used will be 1014 and 1249, respectively.	A pooled efficacy analysis of subjects in protocols 001 and 002 will be conducted to assess more precise estimates of efficacy, with a smaller confidence interval. The pooled efficacy analysis will be governed by a separate Statistical Analysis Plan.	To clarify pooled analysis will be described in a separate plan	None
Throughout protocol		Administrative edits	For clarity and consistency	None
Amendment 3				
6.2 Inclusion Criteria	• Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA, of 25 to 67 letters read (approximately 20/50 to 20/320 Snellen equivalent) in the study eye. …. • Study eye must: o Have active leakage on Fluorescein Angiogram involving the fovea o Have edema involving the fovea o Be free of foveal scarring o Be free of foveal atrophy	• Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA, of 25 to 67 letters read (approximately equivalent to 20/50 to 20/320 Snellen) in the study eye. …. ETDRS BCVA ≥ 20 letters read (approximately equivalent to 20/400 Snellen) in the fellow eye. • Study eye must: o Have active leakage on Fluorescein Angiogram involving the fovea o Have edema involving the fovea as measured by central subfield foveal thickness on SD-OCT o Be free of scarring within 2 disc diameters of the fovea o Be free of atrophy within 2 disc diameters of the fovea	To broaden the allowable vision criteria, ensure patients with monocular vision are not included and to clarify distance to the fovea for atrophy and scarring	None

6.3 Exclusion Criteria	The use of an effective contraception method should continue for 4 months post-injection of the investigational product, in line with the follow-up period of the study.	The use of an effective contraception method should continue for 6 months post-injection of the investigational product, in line with the follow-up period of the study.	To ensure contraception is maintained for 6 months post-injection; consistent with the IB language	None; this language is accurate in current consent forms
5.4 Safety Endpoints		The incidence of positive serum antibodies to ONS-5010	To add a PK endpoint	None
9.3.5 Serum samples for antibodies to ONS-5010 and measurement of ONS-5010 concentrations		Approximately 5 subjects randomized to the ONS-5010 arm will undergo serum sampling for pharmacokinetic (PK) and immunogenicity testing at approximately 2 selected sites. The selection of patients who will take part in the PK and immunogenicity testing will be restricted to those receiving monocular ONS-5010 treatment **in the study eye only**, with no anti-VEGF treatment **of any kind** in the fellow eye. Serum samples for analysis of antibodies to ONS-5010, and ONS-5010 concentration measurement will be collected at Day 0, Day 1, Day 2, Day 3 and Day 4. Further serum samples for analysis of antibodies to ONS-5010 will be collected at Day 30, Day 31, Day 32, Day 33 and Day 34. Masking will be maintained by informing all subjects that they may be randomly selected for serum sampling.	To collect serum samples for evaluation of ONS5010 and ONS5010 antibodies in the serum of subjects at select sites	Increased risk of additional blood draws
4.1 Study Overview	Approximately 30 study sites	Approximately 40 study sites	To increase the number of sites in order to ensure tiemley enrollment	None
Throughout protocol	Australia and New Zealeand specific language	Removed references to Australia and New Zealand and to region as a statistical covariate in the analysis	The study is only being conducted in the US	None
Throughout protocol		Administrative edits	For clarity	None