Clinical Protocol ONS-5010-003

Project:	ONS-5010
Compound Number/Name:	bevacizumab intravitreal injection
Protocol Number:	ONS-5010-003
Phase:	3
IND Number:	138373
NCT Number:	NCT04516278
Protocol Title:	A 3-MONTH STUDY TO ASSESS THE SAFETY OF ONS-5010 IN SUBJECTS WITH VISUAL IMPAIRMENT DUE TO RETINAL DISORDERS, NORSE THREE
Sponsor:	Outlook Therapeutics, Inc 4260 US Route 1 Monmouth Junction, NJ 08852
Medical Monitor:	Bart Chapman, MD
Issue Date:	Version 1.0, 28JUL2020

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Approval:

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7/28/2020
Date

Jennifer M. Kissner, Ph.D.
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7/28/2020
Date

Terry Dagnon, MS
Chief Operating Officer

CONFIDENTIAL

This protocol contains confidential information about a product provided by Outlook Therapeutics, Inc. This information is provided for the exclusive use of the Investigators participating in this study. Any and all confidential information contained herein may not be disclosed to any other person or party without the prior written consent of Outlook Therapeutics, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ONS-5010. I have read the ONS-5010-003, NORSE THREE protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone number
Medical Monitor (24-Hour emergency contact)	Dr. Bart Chapman	1-469-810-0620 bart.chapman@greenlightclinical.com
Sponsor Clinical Lead	Kathleen Billman	1-678-469-2585 kathleenbillman@outlooktherapeutics.com
Principal Investigator	The Coordinating Principal Investigator will be appointed by the Sponsor before the end of the study. As part of his or her responsibilities, the Coordinating Principal Investigator will review the final Clinical Study Report and will sign the report to confirm that it accurately describes the conduct and results of the study.	

2. SYNOPSIS

Name of Sponsor/Company: Outlook Therapeutics, Inc	
Name of Investigational Product: ONS-5010	
Name of Active Ingredient: bevacizumab intravitreal injection	
Title of Study: A 3-month study to assess the safety of ONS-5010 in subjects with visual impairment due to retinal disorders, NORSE THREE	
Study center(s): approximately 20 study centers in the US	
Protocol Number: ONS-5010-003	
Studied period: 7 Month Duration Estimated date first subject enrolled: September 2020 Estimated date last subject completed: March 2021	**Phase of development:** Phase 3
Objectives: **Primary:** To conduct a descriptive statistical analysis of the frequency and incidence of adverse events following three intravitreal injections of ONS-5010 **Secondary:** To evaluate changes in safety parameters following intravitreal injections of ONS-5010	
Number of subjects (planned): Approximately 180	
Diagnosis and main criteria for inclusion: Patients with retinal disorders who benefit from treatment with bevacizumab intravitreal injections, including those with neovascular age-related macular degeneration, branch retinal vein occlusion, or diabetic macular edema	
Investigational product, dosage, and mode of administration: 1.25 mg (in 0.05 ml of solution) of ONS-5010 by intravitreal injection every month for 3 months	
Criteria for evaluation: The primary endpoint is the frequency and incidence of treatment-emergent adverse events following monthly intravitreal injections of ONS-5010	
Statistical methods: No formal inferential statistics will be performed on safety assessments. Statistical methods for the safety analyses will be primarily descriptive in nature. The number and percent of participants reporting each treatment-emergent AE will be summarized descriptively, as well as the number and percent of treatment-emergent Ocular AEs. The proportion of subjects who lose fewer than 15 letters in BCVA score at Day 90 compared to baseline will be reported. The proportion of subjects with a visual acuity of 35 letters or worse at Day 90 will also be reported. Missing or incomplete AE onset dates will be imputed as needed to determine treatment-emergence, defined as occurring between first dose and Day 90. Missing BCVA data will not be imputed.	

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BRVO	Branch retinal vein occlusion
CATT	Comparison of AMD Treatments Trials
CNV	Choroidal neovascularization
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DME	Diabetic macular edema
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
HRVO	Hemiretinal vein occlusion
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1 antibody
IND	Investigational New Drug
IOP	Intraocular pressure
IRB	Institutional Review Board
NCI	National Cancer Institute
PCV	Polypoidal choroidal vasculopathy
RVO	Retinal vein occlusion
SAE	Serious adverse event
SD-OCT	Spectral-domain optical coherence tomography
TEAEs	Treatment-emergent adverse events
US	United States
VEGF	Vascular endothelial growth factor
YAG	Yttrium aluminium garnet

5. INTRODUCTION

Outlook Therapeutics is developing ONS-5010, an ophthalmic specific bevacizumab, for intravitreal injection in patients with retinal conditions requiring anti-vascular endothelial growth factor (VEGF) therapy.

At present, Avastin®, the marketed bevacizumab product, is not specified for use in ophthalmic indications; however, it is widely used off-label, injected intravitreally for the treatment of neovascularizing eye diseases, specifically age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (Elman, 2012; Martin, 2012; Nguyen, 2012; Ogura, 2014).

ONS-5010 is intended to provide bevacizumab with a consistent protein concentration, at an appropriate volume in single-use packaging, for use in an ophthalmic setting.

5.1. Disease Background

Neovascular 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, 2010; Rein, 2009; Smith, 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, 2004).

AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form (Ferris, 1984; Lim, 2012; Miller, 2013). Neovascular, or "wet" AMD is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium or subretinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (Ferris, 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, 2007; Shah, 2009). Without treatment most affected eyes will have poor central vision (20/200) within 12 months (Blinder, 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-VEGF treatments (Ferris, 1983; Sommer, 1991; Wong, 2008).

Diabetic Macular Edema

Diabetic retinopathy remains the major threat to sight in the working age population in the developed world. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. Macular edema within 1 disc diameter (1.5 mm) of the fovea is present in 9% of the diabetic population (Arevalo, 2009).

Although visual loss secondary to proliferative changes is more common in subjects with type 1 diabetes, visual loss in subjects with type 2 diabetes is more commonly due to macular edema (Arevalo, 2007).

DME is caused by excessive vascular permeability, driven by increased levels of VEGF resulting in the leakage of fluid and plasma constituents, such as lipoproteins, into the retina, leading to its thickening and ultimately, loss of vision (Das, 2015). As VEGF levels are elevated in the

vitreous of eyes with diabetic retinopathy, anti-VEGF treatment is an attractive therapeutic modality in the treatment of DME.

Branch Retinal Vein Occlusion

Retinal vein occlusion (RVO) is the second leading retinal vascular disorder leading to vision loss. RVO can be classified into two categories depending on where the occlusion occurs. An occlusion at the central retinal vein is classified as a central retinal vein occlusion, while a blockage at the arteriovenous crossing is termed a branch retinal vein occlusion (BRVO).

The two main vision compromising complications of retinal vein occlusion are macular edema, and retinal ischemia leading to iris and retinal neovascularization. These complications result in an increased secretion of VEGF by endothelial cells, resulting in neovascularization (Bowers, 1987). These complications may lead to neovascular glaucoma, vitreous hemorrhage, and tractional retinal detachment (depending on where the neovascularization occurs), with severe visual impairment. 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 can result in progressive, severe, and irreversible vision loss (Shah, 2007; Shah, 2009).

Subjects with BRVO have a good prognosis even without treatment, with 50-60% of subjects reporting a final visual acuity of 24/40 or better. However, treatment with photocoagulation or VEGF inhibitors results in better outcomes after six months of treatment (Gallego-Pinazo, 2012).

5.2. Scientific Rationale

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 CNV, and macular edema, causing visual impairment in diabetes and retinal vein occlusion.

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively binds with high affinity to all isoforms of human VEGF and neutralizes VEGF's biological activity. Injected intravitreally, bevacizumab promotes marked regression of intraocular neovascularization in clinical studies of neovascularizing ocular disease (Avery, 2006, Rich, 2006, Yoganathan, 2006). Further, bevacizumab has been demonstrated to have positive clinical effects in the management of DME and BRVO (Yilmaz, 2011; Wu, 2009).

Bevacizumab has been demonstrated to be as effective as ranibizumab in the treatment of AMD, BRVO, and DME; however, it is not licensed for use in these indications, 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.

This study will evaluate the safety of ophthalmic bevacizumab in subjects diagnosed with a retinal condition that would benefit from treatment with intravitreal injection of bevacizumab,

including exudative age-related macular degeneration, diabetic macular edema, or branch retinal vein occlusion.

5.3. Description of Investigational Product

ONS-5010 is a recombinant humanized monoclonal IgG1 antibody (93% human, 7% murine sequences - molecular weight 149 kDa) specific for VEGF binding. It is a colorless to slight brown, opalescent liquid.

Additional information regarding ONS-5010 is available in the Clinical Investigator's Brochure.

5.4. Summary of Clinical Experience and Justification of Dose Selection

The safety and efficacy of intravitreal anti-VEGF therapy for wet AMD, DME, and BRVO 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 United States and European Union sourced Avastin®. ONS-1045 is the active drug substance in the investigational drug product, ONS-5010 that will be administered in this study.

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, 2011).

ONS-5010 is being studied in two ongoing, masked clinical trials in humans. The dose being administered in this study is identical to the dose used in the two ongoing trials. Safety reviews of the masked data in the ongoing trials have been consistent with that published for off-label, intravitreal Avastin use and with the prescribing information provided for Lucentis.

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

Additional information regarding clinical experience with ONS-5010 administered intravitreally is available in the Investigator's Brochure.

6. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study will be to evaluate the safety of ophthalmic bevacizumab in subjects diagnosed with a retinal condition that would benefit from treatment with intravitreal injection of bevacizumab, including: exudative age-related macular degeneration, diabetic macular edema, or branch retinal vein occlusion.

6.1. Primary Objective

The primary objective of the study is to conduct a descriptive statistical analysis of the frequency and incidence of treatment-emergent adverse events following three intravitreal injections of ONS-5010.

6.2. Secondary Objective

The secondary objective of the study is to evaluate changes in safety parameters, as described in Section 11, following intravitreal injections of ONS-5010.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a prospective, multi-center, open label, non-randomized study of intravitreally administered ONS-5010. Approximately 180 subjects with retinal disorders who would benefit from treatment with bevacizumab intravitreal injections will be enrolled at approximately 20 study sites. The study will enroll both treatment naïve as well as previously treated subjects.

Subjects will receive 1.25 mg (in 0.05 ml of solution) of ONS-5010 by intravitreal injection every month for 3 months at 3 time points (Day 0, Day 30, and Day 60), with a follow-up at 90 days (End of Study visit).

Subjects will be assessed via study procedures outlined in the Time and Events Schedule.

7.2. Endpoints

7.2.1. Primary Endpoint

The primary endpoint is the frequency and incidence of treatment-emergent adverse events following three intravitreal injections of ONS-5010.

7.2.2. Secondary Endpoints

Secondary endpoints include the following:

- Intraocular pressure
- Slit lamp biomicroscopy
- Indirect ophthalmoscopy
- Imaging parameters
- Best corrected visual acuity
- Laboratory assessments
- Vital signs

7.3. Number of Subjects

Approximately 180 subjects with either Neovascular AMD, DME, or BRVO will be enrolled into the study.

7.4. Treatment Assignment

This study is a non-randomized study, so eligible subjects will be assigned to receive ONS-5010 at the prescribed dose and frequency as noted in the Time and Events Schedule.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

Individuals are eligible for participation in this study if s/he meets all of the following criteria:

1. Has an active clinical diagnosis and OCT confirmation of one of the following retinal disorders: exudative age-related macular degeneration, diabetic macular edema, or branch retinal vein occlusion (including HRVO) and, in the opinion of the Investigator, requires treatment with an anti-VEGF therapy
2. At least 18 years of age
3. Understands the language of the informed consent; willing and able to provide written informed consent prior to any study procedures; willing to comply with the instructions and attend all scheduled study visits

8.2. Exclusion Criteria

8.2.1. Ophthalmic Exclusion Criteria

An individual is ineligible for participation in this study if s/he meets any of the following criteria:

1. Previous use of approved anti-VEGF or Avastin® within 4 weeks of Day 0, in the study eye. Note the use of Lucentis®, Eylea® or Avastin® are allowed so long as there is at least a 4 week wash out period and the subject continues to need anti-VEGF therapy, in the opinion of the Investigator
2. Macular edema due to something other than exudative AMD, DME or BRVO, in the study eye (e.g., post-cataract surgery, vitreomacular traction, etc)
3. History of inadequate response to previous intravitreal anti-VEGF therapy
4. Neovascularization of the optic nerve or retina, in the study eye, for any reason, including: proliferative diabetic retinopathy and ischemic vein occlusion
5. History of rubeosis irides, in the study eye
6. History of any intraocular or periocular corticosteroid injection or implant, in the study eye
7. Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy within 4 weeks of Day 0, in the study eye; treatment with verteporfin in the non-study eye < 7 days of Day 0
8. Previous subfoveal focal laser photocoagulation within 4 weeks of Day 0, in the study eye; laser photocoagulation (juxtafoveal or extrafoveal) within 4 weeks of Day 0, in the study eye
9. History of vitrectomy, macular surgery, or glaucoma surgery in the study eye; history of submacular surgery or other surgical intervention for retinal conditions in the study eye
10. Ocular surgery in the study eye, within 4 months of Day 0; surgical eyelid procedures on the study eye, within 6 weeks of Day 0
11. Any concurrent intraocular condition in the study eye (e.g., cataract) that, in the opinion of the Investigator, could either
    a. Require medical or surgical intervention, other than protocol treatment, during the study period to prevent or treat visual loss that might result from that condition, or

b. If allowed to progress untreated, could likely contribute to clinically significant vision loss during the study period

12. Active intraocular inflammation in the study eye
13. Current vitreous hemorrhage in the study eye
14. Polypoidal choroidal vasculopathy (PCV) in the study eye
15. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
16. History of idiopathic, infectious, or autoimmune-associated uveitis/ choroiditis, in either eye
17. Current ocular or periocular infection, such as conjunctivitis, keratitis, scleritis, or endophthalmitis, in either eye
18. Aphakia or absence of the posterior capsule in the study eye
19. Previous violation of the posterior capsule in the study eye is also excluded unless it occurred as a result of yttrium aluminium garnet (YAG) posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
20. 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 staphyloma and lacquer cracks
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. ETDRS BCVA < 20 letters read in either eye, or monocular

8.2.2. General Exclusion Criteria

Individuals are not eligible for participation in this study if s/he meets any of the following criteria:

25. Female subjects who are pregnant, lactating, or planning a pregnancy. Females of childbearing potential must agree to submit to a pregnancy test at screening and agree to use an acceptable method of contraception throughout participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicide or diaphragm with spermicide), hormonal methods (oral contraceptives, implantable, transdermal, or injectable contraceptives), or an intrauterine contraceptive device with a documented failure rate of less than 1% per year. Abstinence may be considered an acceptable method of contraception at the discretion of the Investigator, but the subject must agree to use one of the acceptable birth control methods if she becomes sexually active
26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications
27. Subjects who may need or have received systemic anti-vascular endothelial growth factor for oncology in the past year

28. Current treatment for a serious active systemic infection
29. Known allergy to any component of the study drug, not amenable to treatment
30. Previous participation in any studies of investigational drugs within 4 weeks of Day 0 (excluding vitamins and minerals)
31. Inability to comply with study or follow-up procedures

8.3. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time and for any reason without obligation. Subjects may be removed from the study at the Investigator's discretion.

Subjects who withdraw prematurely from the study will be asked to complete study assessments at the Early Termination Visit. If a serious adverse event (SAE) is unresolved at the time of the subject's final study visit, the Investigator should make every attempt to follow-up until the SAE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution.

8.4. Visit Procedure Descriptions

8.4.1. General Procedures

The study will consist of up to 4 study visits over approximately of 3 months. Subjects are expected to attend all study visits.

8.4.2. Visit 1 – Screening / Enrollment (Day 0 to +3)

At Visit 1, subjects will be screened for eligibility. During Visit 1, the following procedures will be performed by study staff:

1. Obtain written informed consent
2. Assign subject number
3. Collect demographics, medical and ocular history
4. Review current and prior concomitant medications
5. Check vital signs
6. Review of body systems
7. Conduct urine pregnancy test on women of childbearing potential
8. Obtain laboratory samples (hematology, chemistries, urinalysis)
9. Obtain best corrected visual acuity
10. Obtain IOP
11. Conduct slit lamp examination
12. Conduct dilated indirect ophthalmoscopy
13. Perform SD-OCT examination
14. Verify subject eligibility based on Inclusion/Exclusion requirements

15. Administer ONS-5010 (in case the Investigator is unable to administer the study treatment on the day of the assessments for some reason, the treatment may be administered within +1 to +3 days (considered the same visit) following the assessment
16. Perform post-treatment safety check
17. Assess for Adverse Events

8.4.3. Visit 2 – Month 1 (Day 30 ± 7 days)

The following procedures will be performed by study staff:

1. Review changes to concomitant medications
2. Check vital signs
3. Obtain best corrected visual acuity
4. Obtain IOP
5. Conduct slit lamp examination
6. Conduct dilated indirect ophthalmoscopy
7. Perform SD-OCT examination
8. Administer ONS-5010
9. Perform post-treatment safety check
10. Assess for adverse events (AEs)

8.4.4. Visit 3 – Month 2 (Day 60 ± 7 days)

The following procedures will be performed by study staff:

1. Review changes to concomitant medications
2. Check vital signs
3. Obtain best corrected visual acuity
4. Obtain IOP
5. Conduct slit lamp examination
6. Conduct dilated indirect ophthalmoscopy
7. Perform SD-OCT examination
8. Administer ONS-5010
9. Perform post-treatment safety check
10. Assess for Adverse Events

8.4.5. Visit 4 / End of Study – Month 3 (Day 90 ± 7 days) or Early Termination

The following procedures will be performed by study staff:

1. Review changes to concomitant medications
2. Check vital signs
3. Review of body systems
4. Conduct urine pregnancy test on women of childbearing potential
5. Obtain laboratory samples (hematology, chemistries, urinalysis)
6. Obtain best corrected visual acuity
7. Obtain IOP
8. Conduct slit lamp examination
9. Conduct dilated indirect ophthalmoscopy
10. Perform SD-OCT examination
11. Assess for Adverse Events

8.4.6. Unscheduled Visit

To ensure subject safety during the study, any subject who requires additional follow-up or treatment for any reason at any time during the study that does not fall on a scheduled study visit should have that visit recorded as an Unscheduled Visit.

9. TREATMENT OF SUBJECTS

9.1. Treatments to be Administered

Subjects who meet screening inclusion and exclusion criteria will receive 1.25 mg ONS-5010, delivered as a 0.05 mL intravitreal injection, monthly, for three consecutive months.

9.2. Study Eye Determination

The study eye will be the eye receiving 1.25 mg ONS-5010. The determination of the study eye will be based on Screening/Baseline information and will be determined prior to treatment.

If both eyes meet study criteria, then the right eye should be designated as the study eye. The eye that is not designated as the study eye will be denoted as the fellow eye.

9.3. Treatment of the Fellow Eye

Subjects may have bilateral disease, but only one eye will be designated the study eye and treated under this protocol.

Local therapies are permitted for the fellow eye during the course of this trial. The choice of local ocular therapy for the fellow eye is not subject to the requirements of this protocol. Medications used for therapy of the fellow eye will be recorded in the subject's medical chart and the case report form (CRF).

9.4. Additional Treatment

If at any time during the study a subject is considered at immediate risk for a vision-threatening event, the Investigator should immediately follow best medical practice in the Investigator's judgment for treating the subject. All additional therapy will be recorded in the subject's medical chart and the CRF.

Subjects will not be discontinued from the study due to initiation/change in a prohibited medication.

9.5. Concomitant Medications

The Investigator should instruct the subject to notify the study site about any new medications s/he 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 CRF. 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 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.

9.6. Treatment Compliance

No study drug will be dispensed to subjects; subject treatment compliance is not applicable.

9.7. Randomization and Masking

This study is neither randomized nor is the study treatment masked. Investigators, study staff, subjects, and the Sponsor will be aware of the investigational treatment provided to the subject.

9.8. Early Discontinuation of Study Treatment

A subject 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:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the Investigator would be in the best interest of the subject 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 subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects 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.

9.9. Withdrawal of Participants from the Study

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

All subjects 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 subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

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

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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

Additional information regarding ONS-5010 is available in the Investigator's Brochure.

10.2. Study Drug Packaging and Labeling

ONS-5010 will be provided in a labeled carton containing 1 single-use pre-labeled, 2-cc glass 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 one 5-micron, blunt 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 and will be labeled "for investigational use only".

10.3. Study Drug Storage

Kits should be stored refrigerated at 2 - 8 °C (36 - 46 °F) in the original carton until time of use to protect from light.

Temperature indicators that can reliably indicate to the receiving party if the lower or upper temperature limits specified for storage 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.

10.4. Study Drug Preparation

The protective cover should be removed from the vial and the top of the vial cleaned with an alcohol wipe. The filter needle, attached to the 1 mL syringe should be used to withdraw the vial contents, using aseptic technique. The filter needle should be replaced with the 30-guage injection needle and any air should be removed while depressing the plunger to the 0.05 mL mark on the syringe.

Additional preparation instructions can be found in the Pharmacy Manual.

10.5. Administration

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.

Additional administration instructions can be found in the Manual of Procedures.

10.6. Study Drug Accountability

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

Accountability will be ascertained by performing reconciliation between the number of study drug cartons (kits and components) sent to the site and the number used and unused at the time of reconciliation. Accurate records of receipt and disposition of the study drug and injectors (e.g., dates, quantity, subject number, kits used, and kits unused) must be maintained by the Investigator or his/her designee.

10.7. Study Drug Handling and Disposal

At the end of the study and after study drug kit accountability has been verified, all study drug (used and unused vials) will be returned to the Sponsor (or designee) or destroyed at the site and documented according to the site's standard process. All study drug accounting procedures must be completed before the study is considered complete.

11. ASSESSMENTS OF SAFETY

For additional information on an assessment, see the Manual of Procedures.

11.1. Best Corrected Visual Acuity

BCVA will be evaluated by ETDRS using standardized lighting and lanes. The results will be reported as the score calculated based on the number of letters read following refraction. Visual acuity testing should precede any examination requiring contact with the eye.

In order to provide standardization and well-controlled assessments of BCVA during the study, all BCVA assessments must be performed by trained staff using well maintained visual acuity equipment/lanes.

11.2. Central Subfield Thickness as Measured by Spectral Domain Optical Coherence Tomography

Retinal thickness and disease characterization will be assessed via spectral domain – optical coherence tomography (SD-OCT). The SD-OCT instrument should be well maintained, and the technician trained and experienced in capturing images. The technician is encouraged to use the same equipment throughout the subject's study participation. All images should be taken by the same technician, whenever possible, on each subject per research site.

11.3. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy, including magnification, will be performed consistent with standard clinical practice. This procedure should be conducted in the same manner for all subjects and will include an assessment of each of the following as normal or abnormal: eyelids, conjunctiva/sclera, cornea, anterior chamber, iris, and lens. All abnormal findings will be described.

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

11.4. Intraocular Pressure

Intraocular pressure will be measured per the study site's regular practice and recorded in the appropriate study document in mmHg. The technician is encouraged to use the same tonometry method throughout the subject's study participation.

11.5. Dilated ophthalmoscopy

Dilated ophthalmoscopy should be performed according to the Investigator's standard procedure. This procedure should be the same for all subjects observed at the Investigator's site. The fundus will be examined thoroughly, and the following variables will be assessed as normal or abnormal (including but not limited to): vitreous, retina, choroid, and optic nerve/disc, appearance of vessels, presence/absence of neovascularization.

11.6. Resting Heart Rate and Blood Pressure

Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same arm each time) will be measured at every visit after the subject has rested for about 5 minutes.

11.7. Review of Body Systems

A review of body systems will include an assessment of each of the following as normal or abnormal: skin, cardiovascular, respiratory, neurological, and musculoskeletal systems. All abnormal findings will be described.

11.8. Laboratory Measurements

Non-fasting clinical laboratory tests will be performed. These laboratory tests include serum chemistry, hematology, and urinalysis, and are to evaluate any underlying disease condition.

Sample handling will be conducted according to the Laboratory Manual.

11.8.1 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.

11.8.2 Blood Chemistry Profile

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO_2, 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.

11.8.3 Pregnancy Test

Pregnancy tests will be performed on all females of childbearing potential. Urine or serum pregnancy tests may be performed locally.

11.8.4 Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, 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.

11.9. Adverse and Serious Adverse Events

11.9.1. Definition of Adverse Events

11.9.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition after or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has signed consent, before treatment, during treatment, or during the study participation, whether or not they are related to the study, must be recorded.

11.9.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or placebo, that fulfils one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Note: Hospitalization is not considered an SAE if it 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

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or during study participation, whether or not they are related to the study, must be recorded.

11.9.2. Relationship to Study Drug

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

11.9.3. Recording Adverse Event

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the signing of the consent form until the end of the study. Serious adverse event information will be collected from signing of the consent form until the end of study participation. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, seriousness outcome (if applicable), and whether or not it caused the subject to discontinue the study.

11.9.4. Intensity

The intensity of each AE will be graded by the Investigator, guided by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. The criteria can be accessed at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

The term "severe" is a measure of intensity. A severe AE is not necessarily an SAE.

Grade refers to the intensity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of intensity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of the hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.9.1.2. An AE of severe intensity may or may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the provided pregnancy form. Pregnancy, in itself, is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.9.5. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the consent form until the end of study participation. Any SAEs considered related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Outlook Therapeutics, or its designee, within one business day of the first awareness of the event. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to Outlook Therapeutics, or its designee.

Additional follow-up information, if required or available, should be faxed to Outlook Therapeutics, or its designee, within one business day of receipt. The information should be recorded on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Outlook Therapeutics is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15-Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs.

11.9.6. Follow-up of AEs and SAEs

All AEs and SAEs reported during study conduct must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. Subjects will be followed for any treatment-related SAEs reported at the end of participation until the condition stabilizes, the event is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent.

NOTE: "Resolution" means the subject has returned to baseline state of health, or the Investigator does not expect any further improvement in the subject's condition or does not expect worsening of the AE.

For a non-serious AE that is first identified on the last scheduled contact, the event must be recorded on the AE CRF with the current status noted, but no further follow-up needs to be performed.

Post-Study SAEs: Investigators are not obligated to actively seek SAE information in former study participants; however, any new SAE reported by the subject to the Investigator that occurs after the last scheduled contact, and is determined by the Investigator to be associated with the use of study drug, should be reported to the Sponsor. The Investigator should follow related SAEs identified after the last scheduled contact until the event has resolved or stabilized or the subject is lost to follow-up.

12. STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan will be prepared for this study. The plan will contain a discussion of the statistical methods, a description of any computational algorithms and data handling conventions, and specifications for the data summaries and listings. It will be finalized before database lock.

12.1. Determination of Sample Size and Level of Significance

Approximately 180 subjects will be enrolled in this study.

The sample size is based on the International Conference on Harmonisation requirement for a safety database of at least 300 subjects exposed to the investigational product, for the initial approval of ONS-5010. The data from this study will be combined with the safety database of two additional clinical trials, ONS-5010-001 and ONS-5010-002.

12.2. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition, demographic, and baseline characteristics (age, sex ethnicity, race, height, weight, and body mass index) will be summarized descriptively. Sex, ethnicity, and race will be summarized with frequency counts and percentages. Baseline ocular assessments will be summarized descriptively as well.

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

12.3. Analysis Populations

12.3.1. Safety Population

The safety population is defined as all subjects who are treated with at least one intravitreal injection of ONS-5010.

12.4. Analysis Methods

Safety endpoints are provided in Section 7.2.

12.4.1. Primary Analysis

The primary endpoint is the frequency and incidence of treatment emergent adverse events following monthly intravitreal injections of ONS-5010, with treatment emergent defined as occurring between first dose and Day 90.

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.

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 treatment-emergent 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-subject 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-treatment value) for all post-treatment 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-treatment) for all post-treatment 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.

BCVA scores measured at each visit will be presented in data listings. The mean absolute values and change from baseline values will be summarized overall and by visit, reporting the mean, standard deviation, median, minimum, and maximum. The proportion of subjects who lose fewer than 15 letters in BCVA score at Day 90 compared to baseline will be reported. The proportion of subjects with a visual acuity of 35 letters or worse at Day 90 will also be reported. Summaries will be repeated for the worst post-baseline assessment and the last post-baseline assessment. All BCVA summaries will be presented overall and by presenting disease type.

12.4.2. Secondary Analysis

The number and percent of participants reporting each treatment-emergent ocular AE will be summarized descriptively. A participant with two or more ocular 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 Ocular AEs reported will also be presented. Ocular AEs will also be summarized by severity as well as relationship to study treatment. A by-subject Ocular AE data listing, including verbatim term, preferred term, system organ class, severity, and relationship to study treatment, will be provided.

12.4.2.1. Extent of Exposure

The extent of exposure will be listed.

12.4.2.2. Subgroup analysis

No subgroup analyses will be performed. If warranted, treatment naïve and previously treated subjects may be analyzed separately for descriptive purposes.

12.4.3. Procedure for Accounting for Missing, Unused or Spurious Data

Complete missing or partial dates will be presented in the listings as reported on CRFs. 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 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 BCVA data will not be imputed.

13. DIRECT ACCESS TO SOURCE DOCUMENTS

13.1. Study Monitoring

Before an Investigator can enter a subject into the study, a representative of Outlook Therapeutics will visit the study site (unless waiver criteria are met) to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of Outlook Therapeutics or its representatives; this will be documented in a Clinical Study Agreement between Outlook Therapeutics or designee and the Investigator

During the study, a monitor from Outlook Therapeutics or its representative will have regular contacts with the study site to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Outlook Therapeutics or designee.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Outlook Therapeutics or designee, and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

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

13.3. Institutional Review Boards/Independent Ethics Committees

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

13.4. 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 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 addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The PI/study staff is responsible for knowing and adhering to their IRB requirements.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The progress of the study will be monitored by onsite, written, e-mail, and telephone communications between personnel at the study site and the Sponsor. The Investigator will allow Sponsor monitors, or designee(s), to inspect all CRFs; subject records (source documents); signed Informed Consent Forms; records of study drug receipt, storage, and disposition; and regulatory files related to the study.

At the time of database lock, the clinical database will be audited to ensure accuracy of the data, as well as to provide an estimated error rate for the final, locked database. The audit will involve a comparison of CRF values with values from data listings generated from the clinical database. Values identified as critical safety and efficacy variables will be confirmed for 100% of the subjects. In addition, a random sample of subjects will be selected for which all data values, excluding comment fields, will be checked. The number of subjects whose data will be randomly reviewed will be determined to provide sufficient accuracy for the estimated error rate of the clinical database.

15. ETHICS

15.1. Ethical Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Outlook Therapeutics, or designee, before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Outlook Therapeutics will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation Guideline for GCP, and applicable regulatory requirements.

15.3. Written Informed Consent

The Principal Investigator(s) at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Outlook Therapeutics, and designees, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years after the discontinuance of the test article for investigation or according to local regulation. If it becomes necessary for Outlook Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17. PUBLICATION POLICY

The institutions and Investigators participating in this study shall have no right to publish or present the results of this study without the prior written consent of Outlook Therapeutics.

18. REFERENCES

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19. APPENDICES

APPENDIX A. TIME AND EVENTS SCHEDULE

ONS-5010-003	Screen/ Baseline	Treatment Phase		
	Visit 1	2	3	4
	Day			
	0 to +3	30	60	90/Early Termination [a]
Visit Window (in days)	—	±7	±7	±7
Informed consent	X			
Inclusion/exclusion criteria	X			
Medical and surgical history	X			
Demographics, height, and weight	X			
Concomitant medications and procedures	X	X	X	X
Vital signs	X	X	X	X
Review of body systems	X			X
Urine pregnancy test [b]	X			X
Laboratory samples (hematology, chemistries, urinalysis)	X			X
Best corrected visual acuity [c ,d]	X	X	X	X
Intraocular pressure [c, d]	X	X	X	X
Slit lamp examination [c]	X	X	X	X
Dilated indirect ophthalmoscopy [c]	X	X	X	X
SD-OCT [c]	X	X	X	X
ONS-5010 Administration [e]	X	X	X	
Post-treatment safety check [f]	X	X	X	
Adverse events	X	X	X	X

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

a. For subjects who withdraw early from the study, perform 30 days (±7 days) following the last injection or study visit
b. For women of childbearing potential
c. Perform pre-injection
d. Perform prior to dilating eyes
e. In case the investigator is unable to administer the study treatment on the day of the assessments for some reason, the treatment may be administered within +1 to +3 days (considered the same visit) following the assessment
f. Injecting physician to perform vision check by finger count/hand motion/light perception within 15 minutes post-treatment for study eye only and measure IOP within 30 minutes (± 10 minutes) post-injection in study eye