CLINICAL STUDY PROTOCOL

Title: A Randomized, Double Masked, Placebo Controlled Study Evaluating ORACEA® in Subjects with Geographic Atrophy Secondary to Non-Exudative Age-Related Macular Degeneration

Acronym: TOGA

Protocol No: TOGA-01

Study Drug: ORACEA®

Clinical Phase: Phase II / III

IND Number: 117302

Sponsor and Coordinating Center: University of Virginia
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Version: January 18, 2016

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January 18, 2016

Date
Site Protocol Acceptance Form

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I have carefully read this protocol and agree to conduct the study in accordance with the current protocol and current Good Clinical Practice (GCP) regulations and guidelines and federal and local regulatory requirements.

Site Principal Investigator Name (Print) ___________________________ Site Principal Investigator Signature ___________________________

Site Name (Print) ___________________________ Date ___________________________
# TABLE OF CONTENTS

List of Abbreviations........................................................................................................... 7

1. Introduction .......................................................................................................................... 9
   1.1 Background .................................................................................................................. 9
   1.2 Clinical Experience .................................................................................................... 11
      1.2.1 Clinical Experience with ORACEA® ................................................................. 12
      1.2.2 Long Term Clinical Experience with Subantimicrobial Doxycycline ............... 13

2. Study Objectives and Endpoints ....................................................................................... 14
   2.1 Study Objectives ......................................................................................................... 14
      2.1.1 Primary Objective ............................................................................................. 14
      2.1.2 Secondary Objectives ....................................................................................... 15
   2.2 Study Endpoints ......................................................................................................... 15
      2.2.1 Primary Endpoint .............................................................................................. 15
      2.2.2 Secondary Endpoints ....................................................................................... 15
      2.2.3 Exploratory Endpoints ..................................................................................... 15
      2.2.4 Safety Endpoints .............................................................................................. 16

3. Study Design ..................................................................................................................... 16
   3.1 Overview ..................................................................................................................... 16
   3.2 Rationale for Study .................................................................................................... 16
   3.3 Rationale for Dosage .................................................................................................. 17
   3.4 Description of Study Design ...................................................................................... 17
   3.5 Flowchart of Study Design ......................................................................................... 18

4. Study Population ............................................................................................................... 18
   4.1 Inclusion Criteria ........................................................................................................ 18
   4.2 Exclusion Criteria ........................................................................................................ 19

5. Study Procedures .............................................................................................................. 22
   5.1 Screening / Day 0 Visit .............................................................................................. 22


5.1.1 Randomization.................................................................23
5.1.2 Study Drug Distribution ..................................................24
5.4 Follow-up Telephone Calls: Month 3, Month 9, Month 15, Month 21 (± 14 days) ..........24
5.5 Follow-up Visits: Month 6, Month 12, Month 18, and Month 24 (± 30 days) ..............24
5.6 End-of-Study Visit (30 Days ± 7 days after completion of Month 24 Visit) ....................25
5.7 Unscheduled Visits ..........................................................25
5.8 Early Termination Visit ......................................................26
5.9 Permanent Discontinuation of the Study Drug with Continuation in the Study ..........27
6. Safety Considerations ..........................................................27
6.1 Adverse Drug Reactions ....................................................27
6.2 Drug Interactions .............................................................29
6.3 Safety Plan ..................................................................29
6.3.1 Ophthalmic Examinations .............................................29
6.3.2 Laboratory Assessments ..............................................29
6.3.3 Physical Exam ............................................................31
6.3.4 Querying for Adverse Events .........................................31
6.3.5 Review of Concomitant Medications ................................31
6.3.6 Assessment of Study Drug Compliance ..........................31
6.3.7 Permanent Discontinuation of the Study Drug with Continuation in the Study ......31
6.3.8 Temporary Discontinuation of the Study Drug with Continuation in the Study ......32
7. Concomitant Medications ....................................................32
8. Concurrent Medical Conditions .............................................33
9. Conversion to Exudative Age-Related Macular Degeneration .................................33
9.1 "New" Exudative Age-Related Macular Degeneration .............................................34
9.2 Recurrent Age-Related Macular Degeneration .....................................................34
10. Study Drug Administration ..................................................34
10.1 Study Drug .................................................................34
10.2 Study Drug Storage .......................................................35
10.3 Study Drug Accountability .................................................................35
10.4 Randomization and Study Drug Assignment ......................................35
10.5 Study Drug Masking ........................................................................36
11. Emergency Unmasking of Subject Treatment Assignment ..................36
12. Subject Withdrawals and Subjects Lost to Follow-up ............................37
   12.1 Subject Withdrawals ...................................................................37
   12.2 Subjects Lost to Follow-up ..........................................................38
13. Rules for Termination of the Study ......................................................38
14. Adverse Events ..................................................................................38
   14.1 Adverse Event (AE) Definition .......................................................38
   14.2 Serious Adverse Event (SAE) Definition .........................................39
   14.3 Recording of Adverse Events (AEs) and Serious Adverse Events (SAEs) .................................................................39
   14.4 Adverse Event (AE) and Serious Adverse Event (SAE) Severity Definitions .................................................................40
   14.5 Adverse Event (AE) and Serious Adverse Event (SAE) Relationship to Study Drug Definitions .................................................................40
   14.6 Adverse Event (AE) and Serious Adverse Event (SAE) Analysis .................................................................41
   14.7 Reportable Events .......................................................................42
15. Data and Safety Monitoring Committee (DSMC) ..................................42
16. Statistical Analysis ............................................................................42
   16.1 Primary Objective and Endpoint ....................................................42
      16.1.1 Power Analysis .....................................................................43
      16.1.2 Details ..................................................................................43
      16.1.3 Power Simulation Results .......................................................43
      16.1.4 Subject Withdrawal ...............................................................44
   16.2 Primary Endpoint Analysis ............................................................44
   16.3 Secondary Statistical Analyses .......................................................46
      16.3.1 Secondary Endpoint #1 Analysis .............................................46
      16.3.2 Secondary Endpoint #2 Analysis .............................................46
      16.3.3 Secondary Endpoint #3 Analysis .............................................47
16.3.4 Secondary Endpoint # 4 Analysis .......................................................... 47
16.3.5 Secondary Endpoint # 5 Analysis .......................................................... 48
16.4 Exploratory Statistical Analyses ............................................................... 48
16.4.1 Exploratory Endpoint # 1 Analysis ....................................................... 48
16.4.2 Exploratory Endpoint # 2 Analysis ....................................................... 48
16.4.3 Exploratory Endpoint # 3 Analysis ....................................................... 49
16.4.4 Exploratory Endpoint # 4 Analysis ....................................................... 49
16.4.5 Exploratory Endpoint # 5 Analysis ....................................................... 49
16.5 Safety Data Analysis ............................................................................... 49
16.6 Missing Data ......................................................................................... 50
17. Regulatory and Ethics Requirements ....................................................... 50
  17.1 Statement on Good Clinical Practice (GCP) Compliance ....................... 50
  17.2 Informed Consent ................................................................................ 50
  17.3 Institutional Review Board (IRB) Review .............................................. 51
  17.4 Protocol Amendments .......................................................................... 52
  17.5 Subject Confidentiality .......................................................................... 52
  17.6 Investigator Responsibilities ................................................................. 52
  17.7 Monitoring and Regulatory Inspections ................................................. 52
  17.8 Data Management Responsibilities, Source Documents and Case Report Forms (CRFs) .... 53
  17.9 Retention of Records ........................................................................... 53
APPENDIX A: Protocol Synopsis .................................................................... 55
APPENDIX B: Study Visit Schedule .............................................................. 59
APPENDIX C: References ............................................................................. 60
APPENDIX D: NEI-VFQ 25 Questionnaire .................................................. 63
APPENDIX E: RCR Model, Mathematical Representation .............................. 74
List of Abbreviations

AE  Adverse Event
ALP  Alkaline Phosphatase
ALT  Alanine amino transferase
AMD  Age-Related Macular Degeneration
ANCOVA  Analysis of Covariance
AREDS  Age-Related Eye Disease Study
AST  Asparate amino transferase
BCVA  Best Corrected Visual Acuity
BUN  Blood urea nitrogen
CFR  Code of Federal Regulations
CNV  Choroidal Neovascularization
CO2  Carbon dioxide, bicarbonate
CRF  Case Report Form
CRP  C-reactive Protein
DSMC  Data and Safety Monitoring Committee
eGFR  Estimated Glomerular Filtration Rate
ESR  Erythrocyte sedimentation rate
ETDRS  Early Treatment Diabetic Retinopathy Study
FA  Fluorescein Angiography
FAF  Fundus Autofluorescence
FDA  Food and Drug Administration
GA  Geographic Atrophy
GCP  Good Clinical Practice
GEE  Generalized Estimating Equation
hCG  Human Chorionic Gonadotropin
HIPAA  Health Insurance Portability and Accountability Act
ICH  International Conference on Harmonization
IDMS  Isotope Dilution Mass Spectrometry
IRB  Institutional Review Board
MCH  Mean cell hemoglobin
MCHC  Mean cell hemoglobin concentration
MCV  Mean cell volume
MDRD  Modification of Diet in Renal Disease
MMP  Matrix metalloproteinase
MTX  Methotrexate
NEI VFQ-25  National Eye Institute Visual Functioning Questionnaire – 25
OCT  Optical Coherence Tomography
PDT  Photodynamic Therapy
RA  Rheumatoid arthritis
RBC  Red Blood Cell
RCR  Random coefficient regression
RCPR  Random coefficient piecewise regression
RDW  Red blood cell distribution width
RPE  Retinal Pigment Epithelial (Epithelium)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SD-OCT</td>
<td>Spectral-Domain Optical Coherence Tomography</td>
</tr>
<tr>
<td>SRP</td>
<td>Scaling and Root Planning</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>WBC</td>
<td>White Blood Cell</td>
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1. **Introduction**

Age-related macular degeneration (AMD) is the primary cause of vision loss and legal blindness in adults over age 60 in the United States. Of the two types of AMD, approximately 90% of cases involve the non-exudative or “dry” form. There are currently no available treatment options for dry AMD; however, a number of studies suggest a significant inflammatory component to the disease. Additional evidence indicates tetracycline derivatives, through their anti-inflammatory effects, may slow the progression of macular degeneration, thus either delaying or preventing further vision loss in this population.

**ORACEA®** (40mg doxycycline – 30mg Immediate Release & 10mg Delayed Release beads), a subantimicrobial dose tetracycline derivative, appears to be well tolerated for the 24-month study Treatment Period, has an excellent safety profile as demonstrated in multiple clinical studies, has efficacy towards inhibition of chronic systemic inflammation, and has demonstrated activity against molecular pathways that are suspected to be important in the evolution of non-exudative age related macular degeneration.

### 1.1 Background

Age-related macular degeneration (AMD) is the leading cause of blindness and visual disability in adults over age 60 in the United States. 20% of the U.S. population aged 65-74 years and 35% of people aged 75 years or more have the disease [1]. AMD is divided into “wet” (exudative or neovascular) and “dry” (non-exudative or atrophic) disease. In the United States alone, 1.6 million new cases of dry AMD and over 150,000 new cases of wet AMD are diagnosed annually [2].

Dry AMD results from the loss and/or dysfunction of retinal pigment epithelial (RPE) cells in the macula, which are critical to the survival of retinal photoreceptors responsible for vision. The loss of RPE cells and subsequent photoreceptors leads to decreased light sensitivity, retinal thinning, and eventual loss of vision. The cause of the breakdown of the RPE layer and loss of photoreceptors remains unclear, but recent evidence suggests inflammation, oxidative stress, as well as other genetic and environmental factors play a critical role [3].

A key pathologic event in development of atrophic AMD is thought to be the accumulation of drusen between the RPE cells and the underlying Bruch’s membrane that separates the RPE from the choroid [4]. The risk of vision loss directly correlates with both the number and size of drusen [5]. Drusen may directly or indirectly lead to loss of RPE cells and photoreceptors. Drusen result in retinal thinning and loss of the protective barrier between the RPE and underlying Bruch’s membrane [6]. This loss of integrity allows for formation of sub-retinal neovascularization leading to development of wet AMD. Anti-vascular
endothelial growth factor (VEGF) therapies are effective in treating the 10% of patients with the neovascular form of AMD [7]. However, there is no treatment or preventative therapy available for the remaining 90% of dry AMD patients [2].

Several factors are now considered important in the initiation and progression of atrophic AMD, including chronic inflammation via complement pathway and macrophage and microglia activation, oxidative stress, programmed cell death, as well as genetic and environmental susceptibility [8]. Tetracycline derivatives are a therapy candidate for atrophic AMD, given their demonstrated ability to target many of these identified pathways that may contribute to the disease [7, 9, 10]. In particular, tetracyclines are known to reduce reactive oxygen species, inhibit matrix metalloproteinase’s (MMPs) that are involved in the breakdown of the barrier between the RPE and Bruch’s membrane, inhibit caspase activation and thereby prevent cell death, prevent complement activation, and inhibit cytokine production through their effects on microglia and T-cell activation [7, 9, 10].

Efficacy of tetracycline derivatives has been demonstrated for both in vitro assays of RPE function and in vivo murine models of retinal disease. Following laser induced choroidal neovascularization (CNV), a model for exudative AMD, mice were fed 0.5 to 50 mg/kg of oral doxycycline in their water. Doxycycline treated mice at all doses demonstrated a > 50% reduction in the volume of laser induced CNV compared to controls (Figure 1) [11]. Minocycline was also found to attenuate photoreceptor degeneration in a mouse model of hemorrhagic neovascular AMD [12]. This effect was thought to be due to a decrease in microglial expression of chemotactic cytokines with a corresponding reduction of subretinal microglial infiltration [12]. In vitro, human RPE cells were protected by minocycline against oxidative damage from both light exposure and oxidative stress [13].

In a pilot study of 18 patients treated over 12 months with reduced-fluence photodynamic therapy (PDT), intravitreal ranibizumab, intravitreal dexamethasone, and oral minocycline to treat neovascular AMD [14], no safety concerns were identified during the course of the study, and stable vision was
maintained in 89% of eyes. Outcomes with reduced-fluence PDT combination therapy were found to be equivalent to prior studies that examined combination therapy that used standard dose PDT with intravitreal ranibizumab alone.

A retrospective analysis of 10 patients with stage 3 or stage 4 non-exudative dry AMD [15] that were receiving treatment with tetracycline or minocycline for rheumatoid arthritis, dermatitis without keratitis, and acne rosacea demonstrated improvement of visual acuity over their one year course of treatment (Figure 2). The authors suggest a protracted course of improvement that started only after 3 to 6 months of treatment, and absence of corneal disease on initial exam, suggest this effect was not due to treatment of ocular rosacea [16, 17].

Among the tetracycline derivatives, doxycycline is an attractive candidate for long-term treatment of inflammation associated with atrophic AMD given a clear dosing split has been identified between its antimicrobial (>100 mg/day) and anti-inflammatory (40 mg/day) properties. Subantimicrobial doxycycline has found widespread clinical use for long-term suppression of acneiform and rosacea skin lesions with treatment effect dependent on its anti-inflammatory rather than antibacterial properties [8]. Subantimicrobial dose doxycycline has also found use in treating chronic periodontitis, proposed as a treatment for abdominal aneurysm, and as an adjunctive treatment in combination with methotrexate for rheumatoid arthritis [18-21]. Studies have shown no alterations in the composition of oral or intestinal microflora for patients receiving long-term subantimicrobial doses of doxycycline [22-24].

1.2 Clinical Experience

ORACEA® is a tetracycline derivative that is approved for treatment of inflammatory lesions of rosacea in adults [25, 26]. Rosacea is a chronic inflammatory disorder with characteristic skin lesions that include redness, visible blood vessels, papules and pustules that appear on the forehead, nose, and cheeks. ORACEA® contains 30mg immediate release and 10mg delayed release beads of doxycycline. The presumed mechanism of action is through reduction of
skin inflammation rather than antimicrobial properties, as 40mg doxycycline is known to be a subantimicrobial dose [27].

1.2.1 Clinical Experience with ORACEA®

Del Rosso et al. compared ORACEA® versus placebo for treatment of rosacea in two (study 301 and 302) phase III, placebo controlled, double blind, randomized multicenter studies [26]. In Study 301, 32% of the subjects were 51 to 70 years of age and 33% in Study 302. In both studies, participants received ORACEA® (n = 269) or placebo (n = 268) once daily for 16 weeks. The mean number of inflammatory lesions at baseline was approximately 20 in both studies. By week 16, study 301 showed a decrease in inflammatory lesions of -11.8 in the treatment versus -9.5 in control groups. In comparison, study 302 showed a decrease of -5.9 compared to -4.3 in treatment versus control group (p<0.001 for both studies).

In both study 301 and 302, ORACEA® was well-tolerated, with no major safety issues identified in the treatment group. For study 301, adverse events were reported in 44% of treatment versus 38.7% of control group participants, with most adverse events rated as mild or moderate in severity. Common adverse events included: diarrhea (4.8% treatment versus 3.3% control), nasopharyngitis (4.4% treatment versus 2.6% control), and headache (4.4% treatment versus 5.9% control). All subjects received hematology and serum chemistry panels at baseline and week 16 with no significant deviations or trends identified during the course of treatment.

A randomized, double-blind, placebo-controlled parallel group study evaluated the efficacy of adjunctive ORACEA® compared to placebo in adult subjects with untreated periodontitis. Subjects were treated by scaling and root planning (SRP) and were assigned to receive either ORACEA® or placebo once daily for 9 months. The study demonstrated ORACEA® as an adjunct to SRP achieved significantly greater clinical benefits compared to SRP alone [28].

Compliance with the once-daily dosing regimen was high (> 92%). ORACEA® was well tolerated, with no clinically meaningful difference in the numbers of adverse events reported by the treatment group compared to the placebo group, including adverse events associated with the genitourinary and gastrointestinal tracts or skin [28]. 88 subjects (66.2%) in the ORACEA® group reported 217 adverse events and the most common were: headache (9.8%) and influenza and nasopharyngitis (5.3% each). 94 subjects (70.7%) in the placebo group reported 229 adverse events and the most common were: sensitivity of teeth (9.8%) and
headache and nasopharyngitis (7.5% each). No adverse event or serious adverse event in either group was evaluated by the investigators to be probably related to the study drug. There were no clinically meaningful differences between the treatment and placebo control groups with respect to laboratory tests (complete blood count and blood chemistry) or changes in laboratory test parameters between baseline and Month 9 [28].

With respect to microbiologic outcomes, the study demonstrates that long-term use of ORACEA® does not result in a change in microbial flora, an increase in doxycycline resistance, the acquisition of doxycycline resistance, or the emergence of cross-resistance or multi-antibiotic resistance [28].

1.2.2 Long Term Clinical Experience with Subantimicrobial Doxycycline

Longer term interventions with subantimicrobial dose doxycycline have also been examined.

A double-blind, placebo-controlled trial that evaluated the intestinal flora in adult subjects with chronic periodontitis demonstrated long-term treatment with subantimicrobial dose doxycycline has no antibacterial effect on intestinal flora. 69 subjects (30 – 75 years of age) were randomized to receive either 20mg doxycycline (subantimicrobial dose) or placebo-control twice-daily for 9 months. Specifically, the results suggest a 9-month regimen of subantimicrobial dose doxycycline does not result in: a change in the normal fecal or vaginal flora, an increase in doxycycline resistance, the acquisition of doxycycline resistance, or the emergence of multi-antibiotic resistance [29].

Four multicenter, placebo-controlled, double-blind, randomized clinical trials evaluated the administration of multiple doses of subantimicrobial dose doxycycline for the treatment of adult periodontitis. In studies 1-3, 437 subjects were randomized to receive placebo, 10 mg doxycycline daily, 20 mg doxycycline daily, or 20 mg doxycycline twice daily for 12 months. In study 4, 190 subjects were randomized to either placebo or 20 mg doxycycline twice daily for 9 months. A meta-analysis of all four studies showed doxycycline was well-tolerated and reported adverse events were similar between the doxycycline groups and placebo control group with no difference in the occurrence of adverse reactions usually associated with higher-dose tetracyclines between the groups [30]. No clinically significant differences were identified for liver or kidney function tests in the treatment groups as compared to the control group and no resistance developed to doxycycline during the course of the study [30].
A randomized, double-blind clinical study compared the efficacy of doxycycline adjunctive to methotrexate (MTX) versus MTX alone in 66 adult subjects (27 – 74 years of age) with early seropositive rheumatoid arthritis (RA). Subjects were randomized to: 100 mg doxycycline (antimicrobial dose) twice-daily plus MTX, 20 mg doxycycline (subantimicrobial dose) twice-daily plus MTX, or placebo plus MTX for a period of two years. Both doxycycline treatment groups exhibited the same reduction in RA severity over the course of the study, and the improvement in both treatment groups was greater than the improvement exhibited by the placebo-control group [21]. Additionally, the number of adverse events reported in the subantimicrobial dose treatment group and the placebo group was equivalent and less than the number of adverse events reported by the antimicrobial dose treatment group [21].

A two year, double-masked, randomized trial compared treatment with 20mg doxycycline (subantimicrobial dose) twice daily versus placebo in 128 post-menopausal women 45 – 70 years age (at the time of screening) with chronic periodontitis. Results showed a statistically significant reduction in serum inflammatory biomarkers hs-CRP and MMP-9 in the treatment versus control group. Notably, there was no sign of microbiological resistance in the treatment group as compared to the placebo group and no significant safety issues were identified during the course of the study [31].

2. Study Objectives and Endpoints

2.1 Study Objectives

This study will assess the efficacy and safety of daily oral administration of ORACEA® compared with daily oral administration of placebo in subjects with geographic atrophy due to non-exudative age-related macular degeneration.

2.1.1 Primary Objective

- Evaluate the efficacy of daily oral administration of ORACEA® compared with placebo control on the rate of change in area of geographic atrophy as measured by the change in area of geographic atrophy.
2.1.2 Secondary Objectives

- Evaluate the safety of daily oral administration of ORACEA® through the collection of adverse events and serious adverse events, vital signs measurement, and ocular and clinical laboratory assessments.
- Evaluate the efficacy of daily oral administration of ORACEA® with respect to visual acuity outcomes, anatomic outcomes, and subject-reported visual functioning outcomes.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- Rate of enlargement in area of geographic atrophy in the study eye during the 24-month Treatment Period (Day 0 – Month 24), as assessed by fundus photography.

2.2.2 Secondary Endpoints

- Change in the rate of enlargement in area of geographic atrophy in the study eye between the six-month Observation Period (Day 0 – Month 6) and the 24-month Treatment Period (Month 6 – Month 30) as assessed by fundus photography.
- Change in Best Corrected Visual Acuity (BCVA) as measured by ETDRS in the study eye at Month 24 as compared to Day 0.
- Change in quality of life as measured by the NEI VFQ-25 at Month 24 as compared to Day 0.
- Proportion of subjects progressing to exudative age-related macular degeneration in the study eye by Month 24 in the ORACEA® group as compared to the placebo group.
- Proportion of subjects progressing to exudative age-related macular degeneration in the fellow eye by Month 24 in the ORACEA® group as compared to the placebo group.

2.2.3 Exploratory Endpoints

- Rate of enlargement in area of geographic atrophy in the study eye during the 24-month Treatment Period (Day 0 – Month 24), as assessed by fundus autofluorescence.
- Change in the rate of enlargement in area of geographic atrophy in the study eye between the six-month Observation Period (Day 0 –
Month 6) and the 24-month Treatment Period (Month 6 – Month 30) as assessed by fundus autofluorescence.

- Rate of enlargement in area of outer retinal disruption in the study eye during the 24-month Treatment Period (Day 0 – Month 24), as assessed by en-face spectral-domain optical coherence tomography (SD-OCT) of the inner segment / outer segment band.

- Change in the rate of enlargement in area of outer segment disruption in the study eye between the six-month observation period (Day 0 – Month 6) and the 24-month Treatment Period (Month 6 – Month 30) as assessed by en-face spectral-domain optical coherence tomography (SD-OCT) of the inner segment / outer segment band.

2.2.4 Safety Endpoints

- Incidence and severity of ocular adverse events.
- Incidence and severity of non-ocular adverse events.
- Changes and abnormalities in clinical laboratory parameters.
- Changes in vital signs.

3. Study Design

3.1 Overview

This is a multicenter, randomized, double-masked, placebo controlled study to evaluate the efficacy and safety of ORACEA® in participants with geographic atrophy secondary to non-exudative age-related macular degeneration. This study consists of a 24-month Treatment Period (Day 0 - Month 24), followed by an End-of-Study Visit, approximately 30 days after completion of the Month 24 visit. Approximately 286 participants will be randomized at investigational centers in the United States to either ORACEA® or placebo for a period of 24 months.

3.2 Rationale for Study

Age-related macular degeneration (AMD) is the primary cause of vision loss and legal blindness in adults over age 60 in the United States [1]. Of the two types of AMD, approximately 10% of cases involve the “wet” (exudative or neovascular) form and 90% the “dry” (non-exudative or atrophic) form. While multiple therapies are approved in the United States for the treatment of “wet” age-related macular degeneration, there is no approved treatment or preventative therapy available for the treatment of “dry” age-related macular degeneration [2].
3.3 Rationale for Dosage

ORACEA® (40mg doxycycline – 30mg Immediate Release & 10mg Delayed Release beads) has been selected based on its demonstrated efficacy towards inhibition of chronic systemic inflammation and its subantimicrobial properties. The study requires once-daily administration which is consistent with the prescribing recommendations for ORACEA®. Additionally, prior studies indicate that long-term daily administration of subantimicrobial dose doxycycline is tolerated in older populations [21, 26, 29, 31].

3.4 Description of Study Design

After providing informed consent, potential subjects will undergo screening (Day 0) to determine if they are eligible to participate in the study. After eligibility is confirmed and the “study eye” is selected, eligible subjects will be randomized in a 1:1 ratio to either the ORACEA® treatment group or placebo treatment group. Approximately 286 eligible subjects (143 per treatment group) are randomized at Day 0 to ensure approximately 214 subjects (107 per treatment group), complete the study Treatment Period and End-of-Study Follow-up Visit.

During the 24-month Treatment Period (Day 0 – Month 24), subjects will return for follow-up study visits every 6 months at Months 6, 12, 18, and 24 (± 30 days). Site staff will be asked to contact the subjects via telephone at Months 3, 9, 15, and 21 (± 14 days). 30 days (± 7 days) after completion of the Month 24 visit, participants will be asked to return for an End-of-Study Follow-up Visit.

Subjects who discontinue prematurely from the study drug treatment will be encouraged to continue to comply with the study visit schedule. Subjects who initiate study drug treatment, and discontinue early from the study will be asked to complete an Early Termination Visit.
3.5 Flowchart of Study Design

4. Study Population

4.1 Inclusion Criteria

**General**
1. Male or female, age ≥ 55 years.
2. If a female of childbearing potential, must agree to use an effective form of contraception for the duration of the study and must have a negative serum pregnancy test at Day 0.
3. Willing and able to sign the informed consent.
4. Willing and able to return for all scheduled study visits and assessments and complete all study-related tests and procedures.

**Ocular Conditions**
5. Best Corrected Visual Acuity (BCVA) of 20/20 – 20/400 in the study eye as measured by ETDRS.
6. Best Corrected Visual Acuity (BCVA) of hand motion or better in the non-study eye as measured by ETDRS.
7. Clinical diagnosis of geographic atrophy secondary to non-exudative age-related macular degeneration in at least one eye (study eye) as confirmed by color fundus photography.
8. Geographic atrophy lesions of $\geq 0.75$ and $\leq 7.0$ MPS disc areas ($\geq 1.995mm^2$ and $\leq 18.62 mm^2$) as measured by fundus photography in the study eye at Day 0.

4.2 Exclusion Criteria

Non-Exudative Age-Related Macular Degeneration Conditions
1. Geographic atrophy in the study eye due to causes other than non-exudative age-related macular degeneration.
2. History of or active presence of choroidal neovascularization secondary to exudative age-related macular degeneration in the study eye as confirmed by optical coherence tomography.
3. History of treatment or expected need for treatment in the study eye for the duration of the study with any anti-angiogenic therapy.
4. History of or active presence of choroidal neovascularization secondary to exudative age-related macular degeneration in the non-study eye requiring any treatment within 12 months (360 days) prior to Day 0 or expected to require treatment for the duration of the study.
5. Prior treatment for non-exudative age-related macular degeneration in either eye (excludes AREDS or other vitamin and mineral supplements).

Prior and Concomitant Ocular Treatments, Procedures, and Conditions
6. Current or any previous history of treatment of the study eye with any tetracycline derivative for any ocular condition.
7. History of treatment with intravitreal, subtenon, or periocular steroids within 180 days prior to Day 0 in the study eye.
8. Any previous history of treatment with photodynamic therapy (PDT) or intravitreal injection with any anti-VEGF agent in the study eye.
9. Any previous history of treatment with photodynamic therapy (PDT) or intravitreal injection with any anti-VEGF agent in the non-study eye within 12 months (360 days) prior to Day 0.
10. History of vitreoretinal surgery, corneal transplant, or laser photocoagulation (e.g. for choroidal neovascularization, diabetic macular edema, and proliferative diabetic retinopathy) in the study eye.
11. Any intraocular or periocular surgery within 90 days prior to Day 0 in the study eye.
12. Any previous filtration surgery in the study eye (e.g. trabeculectomy, trabeculoplasty, or glaucoma drainage implant).

Concurrent Ocular Conditions
13. Active or history of ocular disorders in the study eye that in the opinion of the investigator may confound interpretation of the retina or affect central vision (other than non-exudative age-related macular degeneration), including epiretinal membrane, retinal vein occlusion, neovascular disease such as diabetic retinopathy or diabetic macular edema, retinal detachment, macular hole, and choroidal neovascularization of any cause.
14. Active ocular inflammation (including trace or above) or active ocular or periocular infection within 90 days of Day 0 in the study eye.
15. Active presence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in the study eye.
16. History or active presence of idiopathic or autoimmune uveitis in either eye.
17. Any history or active presence of severe dry eye disease, such as ocular rosacea, significant meibomian gland dysfunction, ocular herpetic infection, and sjogrens syndrome in the study eye.
18. Structural damage to the macula in the study eye, secondary to causes other than non-exudative age-related macular degeneration.
19. History of vitreous hemorrhage in the study eye within 90 days of Day 0.
20. Significant media opacities in the study eye, including cataract, or inadequate pupillary dilation which in the opinion of the investigator, might interfere with visual acuity assessment, assessment of safety, or photography.
21. Concurrent disease in the study eye that in the opinion of the investigator would compromise visual acuity or require medical or surgical intervention during the study period.
22. Aphakia or absence of the posterior capsule in the study eye (unless due to YAG capsulotomy).
23. Refractive error greater than -6.00 diopters or +6.00 diopters in the study eye.
24. Uncontrolled glaucoma or ocular hypertension (defined as IOP > 22mmHg despite treatment with medication) in the study eye.

Tetracycline-Derivative Specific Conditions
25. History of any hypersensitivity to tetracycline components.
26. Use of a tetracycline derivative therapy for a concurrent systemic or ocular disorder within 90 days of Day 0.
27. History of long-term (>6 months within 5 years of Day 0) use of tetracycline therapy for a concurrent systemic or ocular disorder.
28. Concurrent use of anticoagulant therapies (with the exception of ≤ 325 mg aspirin).
29. Concurrent use of penicillins, methoxyflurane, oral retinoids, barbiturates, carbamazepine, and phenytoin.
30. History of sensitivity to the sun.

Systemic Conditions
31. Concurrent or ongoing treatment for any systemic infection within 14 days of Day 0.
32. Laboratory tests indicating significantly impaired renal function (defined as eGFR less than 45 ml/min) or hepatic function (defined as ≥2x ULN).
33. Limited survival prognosis due to active malignancy or history of active malignancy within 5 years of Day 0 (does not include successfully treated (excised) skin or oral cancer, or prostate cancer under active surveillance / observation).
34. Uncontrolled blood pressure (defined as systolic ≥ 180 and/or diastolic ≥ 110).
35. History of myocardial infarction, cerebrovascular accident, transient ischemic attack within 90 days of Day 0.
36. Evidence of significant uncontrolled comorbidity, chronic illness, or condition with a limited survival prognosis (e.g., cancer, severe / unstable cardiovascular disease) that would make participation in the study or adherence to the study schedule and treatment regimen difficult or unlikely.
37. Women who are pregnant or nursing.

Other Conditions
38. Concurrent or previous participation in a study evaluating an investigational drug or device within 30 days prior to Day 0.
5. Study Procedures

The study visit schedule and protocol required assessments and procedures are described in Section 5 and outlined in Appendix B: Study Visit Schedule.

5.1 Screening / Day 0 Visit

The following exams and tests will be completed at the Screening / Day 0 Visit:

- Obtain Written Informed Consent
- Demographics
- Medical, Surgical, and Ocular History Review
- NEI VFQ-25 Questionnaire
- Concomitant Medication Review
- Vital Signs including blood pressure, pulse, and temperature
- Physical Exam
- Refraction and Visual Acuity by ETDRS (Bilateral)
- Comprehensive ophthalmic exam, includes: slit-lamp biomicroscopic exam and dilated fundus exam (Bilateral)
- Color Fundus Photos (Bilateral)
- Optical Coherence Tomography (Bilateral)
- Fundus Autofluorescence (Bilateral / Optional)
- Laboratory Assessments (complete blood count with differential, chemistry profile, and erythrocyte sedimentation rate; serum hCG will be performed in females of child-bearing potential)
- Review Study Inclusion and Exclusion Criteria
- Determination of the Study Eye and Participant Eligibility

Screening / Day 0 assessments may be completed over multiple days / visits, but must be completed within 21 days of signing the informed consent. If a subject completes any of the ophthalmic examinations or tests per standard practice prior to the signing of the informed consent, those examinations or tests may be used to determine the subject’s eligibility if occurring within 21 days of signing of the informed consent.

Subjects who have a history or active presence of exudative “wet” age-related macular degeneration at Day 0 in the study eye will be excluded from participation in this study. Subjects who have a history or active presence of exudative “wet” age-related macular degeneration in the fellow eye at Day 0, but have not received active treatment in the fellow eye within the 12 months prior to Day 0 and are not anticipated to require treatment for the duration of the study, may be enrolled.

A subject must meet all the eligibility criteria at Screening / Day 0 to be considered eligible for randomization in the study.
Determination of the study eye is made by the investigator, and verified by the Boston Reading Center. Only one eye will be chosen as the study eye. The study eye is the eye that meets all of the study eligibility criteria. If both eyes are eligible, the eye with the worse visual acuity as assessed at Day 0 will be the study eye. If the visual acuity in both eyes is the same, the right eye will be the study eye, unless the investigator can provide appropriate justification for selecting the other eye as the study eye.

5.1.1 Randomization

All subjects will be randomized after confirmation of eligibility from the Screening / Day 0 and confirmation of study eye eligibility by the Boston Reading Center. Subjects will be randomized in a 1:1 ratio to ORACEA® capsules or matching placebo capsules, to be taken orally once-per-day daily for 24 months.

It is possible that subjects will be randomized at Screening / Day 0 prior to receipt of the laboratory results. Subjects must be informed that their participation may be terminated in the unlikely event of an exclusionary abnormal test result. If any laboratory test results indicate a medical problem precluding participation after randomization occurs, the subject will be contacted by telephone and asked to immediately discontinue their study drug. Laboratory results that would preclude participation include significantly impaired renal function (defined as eGFR less than 45 ml/min) and hepatic disease (defined as ≥2x ULN).

Randomization Details: The randomization list for each investigational site will be generated at the University of Virginia by the University of Virginia Department of Public Health Sciences, Division of Biostatistics. A combined total of 286 treatment assignments will be generated. The randomization list for each investigational site will be generated via a permuted-block randomization scheme that will require the treatment assignments to be in approximate balance at any point in time during the enrollment period. To avoid assignment discovery, the permuted-block size utilized in generating the randomization list will be random. Each permuted-block of assignments will include an equal number of ORACEA® capsule and matching placebo capsule assignments and the assignments will be sequentially utilized according to the permuted assignment order. The Division of Biostatistics will send the blind-protected (i.e. coded) randomization list for each investigational site to the
Coordinating Center at the University of Virginia, where the lists will be maintained. Blind-protected coded drug kits and matched coded treatment assignments will be sent to the investigational sites. Following study completion, and only after the University of Virginia Coordinating Center central database has been officially locked in preparation for data analysis, will the Division of Biostatistics reveal the treatment assignment code to the investigational sites. A backup, password protected copy of the original randomization list will be stored on the University of Virginia Information Technology and Communication Multi-Tier server. Two Biostatisticians from the University of Virginia, Department of Public Health Sciences, Division of Biostatistics will have access to the password.

5.1.2 Study Drug Distribution

Following confirmation of eligibility, the subject will be given their study drug with instructions for use. The study will utilize 40 mg ORACEA® capsules or matching placebo capsules. Subjects should take one capsule each morning on an empty stomach (defined as at least one hour before or two hours after a meal). Administration of adequate amounts of fluid along with the capsules is recommended to wash down the capsule to reduce the risk of esophageal irritation and ulceration. The subject will continue with the once-daily dosing regimen for the duration of the 24-month Treatment Period.

5.2 Follow-up Telephone Calls: Month 3, Month 9, Month 15, Month 21 (± 14 days)

The site will contact the subject to review potential adverse events, concomitant medications, and study drug compliance.

5.3 Follow-up Visits: Month 6, Month 12, Month 18, and Month 24 (± 30 days)

The following exams and tests will be completed at each follow-up visit:

- Concomitant Medication Review
- Adverse Event Review
- NEI VFQ-25 Questionnaire (Month 12 and 24 only)
- Vital Signs including blood pressure, pulse, and temperature
- Physical Exam (Month 12 and 24 only)
- Refraction and Visual Acuity by ETDRS (Bilateral)
• Comprehensive ophthalmic exam, includes: slit-lamp biomicroscopic exam and dilated fundus exam (Bilateral)
• Color Fundus Photos (Bilateral)
• Fundus Autofluorescence (Bilateral / Optional)
• Optical Coherence Tomography (Bilateral Month 24 only / Bilateral and Optional at Months 6, 12, and 18)
• Laboratory Assessments (complete blood count with differential, chemistry profile, and erythrocyte sedimentation rate; urine hCG will be performed in females of child-bearing potential)
• Study Drug Intake Review
• Collection of empty Study Drug Bottles
• Distribution of Study Drug (Months 6, 12, and 18 only)
• Return of all Study Drug (Month 24 only)

The Month 24 Visit marks the conclusion of the 24-month Treatment Period. Subjects will return all empty study drug bottles and all unused study drug at this visit.

5.4 End-of-Study Visit (30 Days ± 7 days after completion of Month 24 Visit)

The following exams and tests will be completed at the End-of-Study visit:

• Concomitant Medication Review
• Adverse Event Review
• Vital Signs including blood pressure, pulse, and temperature
• Physical Exam
• Refraction and Visual Acuity by ETDRS (Bilateral)
• Comprehensive ophthalmic exam, includes: slit-lamp biomicroscopic exam and dilated fundus exam (Bilateral)
• Color Fundus Photos (Bilateral)
• Fundus Autofluorescence (Bilateral / Optional)
• Optical Coherence Tomography (Bilateral / Optional)
• Laboratory Assessments (complete blood count with differential, chemistry profile, and erythrocyte sedimentation rate; urine hCG will be performed in females of child-bearing potential)

The End-of-Study Visit concludes the subject’s participation in the study.

5.5 Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject’s request or at the discretion of the site investigator or Medical Monitor.
Exams and tests to be performed at the visit will be determined by the investigator and are dependent upon the nature of the visit. At a minimum, the following assessments are required at each Unscheduled Visit:

- Concomitant Medication Review
- Adverse Event Review
- Study Drug Intake Review

5.6 Early Termination Visit

A subject may withdraw from the study at any time. The site investigator or sponsor may also withdraw the subject from the study in the event of an intercurrent illness, adverse event, or other reasons concerning the health or well-being of the subject. The subject may also be withdrawn due to non-compliance with the protocol, a protocol violation, or other administrative reasons.

Subjects who are withdrawn prior to initiating the study drug, do not need to complete an Early Termination Visit. Subjects who are withdrawn after initiating the drug should complete an Early Termination Visit. All tests and procedures required at the Month 24 Visit should be completed at the Early Termination Visit. These tests and procedures include:

- Concomitant Medication Review
- Adverse Event Review
- NEI VFQ-25 Questionnaire
- Vital Signs including blood pressure, pulse, and temperature
- Physical Exam
- Refraction and Visual Acuity by ETDRS (Bilateral)
- Comprehensive ophthalmic exam, includes: slit-lamp biomicroscopic exam and dilated fundus exam (Bilateral)
- Color Fundus Photos (Bilateral)
- Fundus Autofluorescence (Bilateral / Optional)
- Optical Coherence Tomography (Bilateral)
- Laboratory Assessments (complete blood count with differential, chemistry profile, and erythrocyte sedimentation rate; urine hCG will be performed in females of child-bearing potential)
- Study Drug Intake Review
- Return of all Study Drug

Subjects will return all empty study drug bottles and all unused study drug at the Early Termination Visit. The Early Termination Visit (if conducted in place of the End-of-Study Visit) concludes the subject’s participation in the study.
5.7 Permanent Discontinuation of the Study Drug with Continuation in the Study

Subjects may permanently discontinue the study drug (due to subject request or investigator or sponsor discretion) due to intercurrent illness, adverse event, or other reasons concerning the health or well-being of the subject. Subjects who permanently discontinue the study drug should be encouraged to remain in the study (but off the study drug) and to complete all remaining follow-up visits and assessments.

Subjects who develop new exudative age-related macular degeneration in either the study or fellow eye during the Treatment Period will immediately permanently discontinue the study drug. These subjects may receive treatment for their exudative AMD at the discretion of the site investigator, and will be asked to continue to complete all study follow-up visits. Subjects who develop recurrent choroidal neovascularization in the fellow eye during the Treatment Period will be allowed to continue on study drug. These subjects may receive treatment for their exudative AMD at the discretion of the site investigator.

Permanent discontinuation of the study drug is discussed further in Section 6.3.7.

6. Safety Considerations

A summary of known adverse drug reactions and drug interactions associated with ORACEA® and tetracycline derivatives follows as well as plans to mitigate these events during the course of the study. Full prescribing information for ORACEA® is included as Appendix C of this protocol.

6.1 Adverse Drug Reactions

In controlled clinical trials evaluating ORACEA® in adult subjects with mild to moderate rosacea, 537 subjects received ORACEA® or placebo control over a 16 week period. The most commonly reported adverse drug reactions are nasopharyngitis, sinusitis, diarrhea, hypertension, and aspartate aminotransferase (AST) increase [32]. The following table summarizes the selected adverse reactions that occurred in the studies at a rate of ≥ 1% for the active arm [32]:

<table>
<thead>
<tr>
<th>Incidence (%) of Selected Adverse Reactions in Clinical Trials of ORACEA (n=269) vs. Placebo (n=268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
</tbody>
</table>
The following adverse reactions have been observed in patients receiving tetracycline derivatives at higher, anti-microbial doses [32]. Because these events were reported in patients receiving higher doses than required by this study, these events are unlikely, but should be noted:

**Gastrointestinal:** Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (within vaginal candidiasis) in the anogential region. Hepatotoxicity is rare. Esophagitis and esophageal ulcerations are rare and have been reported in patients receiving the capsule forms and occurred when the patient took their medication immediately prior to laying down.

**Skin:** Maculopapular and erythematous rashes and in rare instances exfoliative dermatitis have been reported. Photosensitivity has been observed in individuals taking tetracycline derivatives, but was not observed in participants in clinical studies evaluating ORACEA®.

**Renal toxicity:** An increase in BUN has been reported and appears to be dose-related.

**Hypersensitivity reactions:** Urticarial, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus have been reported.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Congestion</td>
<td>4 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fungal Infection</td>
<td>5 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (5)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>5 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Abdominal Distention</td>
<td>3 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Stomach Discomfort</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Blood Pressure Increase</td>
<td>4 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase Increase</td>
<td>6 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Blood Lactate Dehydrogenase Increase</td>
<td>4 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Blood Glucose Increase</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sinus Headache</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
**Blood:** Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

**Other:** Tetracyclines have been associated with the development of pseudomembranous colitis, tissue hyperpigmentation, autoimmune syndromes, pseudotumor cerebri, drug-resistant bacteria, superinfection (although not observed in clinical studies evaluating ORACEA®), and fetal harm when administered to pregnant women [29].

### 6.2 Drug Interactions

Adverse reactions have been observed during the concurrent use of tetracycline derivatives and anticoagulants, penicillin, methoxyflurane, antacids and iron preparations, low dose oral contraceptives, oral retinoids, and barbiturates and anti-epileptics [32]. Specific recommendations with respect to concurrent use of these medications by study subjects are outlined in Section 7.

### 6.3 Safety Plan

#### 6.3.1 Ophthalmic Examinations

Comprehensive ophthalmic examinations are required at Screening / Day 0 and Months 6, 12, 18, 24, and the End-of-Study Follow-up Visit and include an assessment of best corrected visual acuity and slit-lamp and dilated fundus exams. During the dilated fundus examination, the optic disc will be evaluated for papilledema.

#### 6.3.2 Laboratory Assessments

Laboratory assessments are required at Screening / Day 0 and Months 6, 12, 18, 24 and the End-of-Study Follow-up Visit and include a complete blood count (Hematology) with differential, Comprehensive Metabolic Panel (Chemistry Profile) including liver and renal function tests, and erythrocyte sedimentation rate. For women of child-bearing potential, a serum pregnancy test will be administered at Day 0 and a urine pregnancy test at Months 6, 12, 18, 24, and the End-of-Study Visit. Laboratory assessments will be performed at the site’s local lab and include:

- Complete Blood Count (Hematology) with differential:
Red Blood Cell (RBC) Count  |  Mean cell volume (MCV)  
White Blood Cell (WBC) Count  |  Mean cell hemoglobin (MCH)  
Platelet Count  |  Mean cell hemoglobin concentration (MCHC)  
Hemoglobin  |  Lymphocytes  
Hemotocrit  |  Monocytes  
Basophils  |  Eosinophils  
Neutrophils

- Comprehensive Metabolic Panel (Chemistry Profile):
  | Glucose  | Calcium  
  | Albumin  | Total Protein  
  | Sodium  | Potassium  
  | Carbon dioxide, bicarbonate (CO2)  | Chloride  
  | Blood Urea Nitrogen (BUN)  | Creatinine  
  | Alkaline Phosphatase (ALP)  | Alanine amino transferase (ALT)  
  | Asparate amino transferase (AST)  | Bilirubin  
  | hCG (as required)

To determine the estimated glomerular filtration rate (eGFR) from serum creatinine, the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) Study equation must be utilized. The equation is:

\[
GFR \text{ (mL/min/1.73m}^2) = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})
\]

- Erythrocyte Sedimentation Rate (ESR)

- Urinalysis: Urine Pregnancy (hCG) (as required)

Subjects with clinically significant impaired renal (defined as eGFR less than 45ml/min) or hepatic function (defined as ≥ 2.0 ULN) at Screening / Day 0 will not be allowed to enter the study, and if clinically significant abnormalities are present on laboratory assessments (in particular signs of significantly impaired renal or hepatic function) at follow-up visits, consideration will be given to discontinuing the study drug.

For women of child-bearing potential, laboratory assessments include a serum pregnancy test at Screening / Day 0 and a urine pregnancy test at Month 6 and Months 12, 18, and 24. The pregnancy test must be negative at Screening / Day 0 to be considered eligible for the study and must be negative at all study timepoints if the subject is to continue on
study drug. If a subject becomes pregnant while participating in the study, the study drug will immediately be discontinued.

6.3.3 Physical Exam

A physical exam is required at Screening / Day 0 and Months 12, 24, and the End-of-Study Follow-up Visit. Vital signs will also be measured at Screening / Day 0 and Months 6, 12, 18, 24, and the End-of-Study Follow-Up Visit. Any abnormalities should be recorded.

6.3.4 Querying for Adverse Events

Adverse event querying will occur at all study visits (after initiation of study drug), including unscheduled study visits. Additional tests and examinations may be required depending on the adverse events reported by the subject. All adverse events, regardless of the relationship to the study drug, will be recorded.

6.3.5 Review of Concomitant Medications

A review of concomitant medications will occur at all study visits, including unscheduled study visits. At all study visits, subjects should be reminded of prohibited concomitant medications. Prohibited concomitant medications are discussed in Section 7.0.

6.3.6 Assessment of Study Drug Compliance

At each study visit (scheduled and unscheduled) the Site Investigator or designated site staff will assess the subject's compliance with study drug intake.

6.3.7 Permanent Discontinuation of the Study Drug with Continuation in the Study

Subjects may permanently discontinue the study drug (due to subject request or investigator or sponsor discretion) due to intercurrent illness, adverse event, or other reasons concerning the health or well-being of
the subject. The investigator should discuss the case with the Medical
Monitor prior to making the decision to discontinue the study drug.

The study drug should be permanently discontinued immediately if there is
evidence of any of the following:

- Pregnancy
- Pseudomembranous colitis
- Severe Photosensitivity
- Development of autoimmune disorders
- Renal or liver toxicity (≥ 3.0x ULN)
- Allergic reaction to the study drug

Subjects who permanently discontinue the study drug should be
encouraged to remain in the study (but off the study drug) and to complete
all remaining follow-up visits and assessments.

As described in Section 9, subjects who develop new exudative age-
related macular degeneration in either the study or fellow eye during the
Treatment Period (after Month 6) will immediately permanently discontinue
the study drug. These subjects may receive treatment for their exudative
AMD at the discretion of the site investigator, and will be asked to continue
to complete all study follow-up visits.

6.3.8 Temporary Discontinuation of the Study Drug with
Continuation in the Study

Temporary discontinuation of the study drug may be allowed in the event
of an adverse reaction in which the Investigator identifies a possible
causal relationship to the study drug and further evaluation of the adverse
reaction is required. The study drug may be permanently discontinued or
re-started pending the results of the additional evaluation(s) to determine if
there is a causal relationship. All cases involving a potential temporary
discontinuation or re-starting of study drug should be discussed with the
Medical Monitor.

7. Concomitant Medications

All concomitant medications should be used in accordance with approved labeling and
as prescribed throughout the duration of the study.

Adverse reactions have been observed when tetracycline derivatives are used
concurrently with certain medications. The following medications should not be used by
subjects during their participation in the study:
• Anticoagulants, with the exception of ≤ 325mg aspirin
• Penicillins
• Methoxyflurane
• Oral retinoids, including isotretinoin and acitretin
• Barbiturates, carbamazepine, and phenytoin

Other than the study drug, concurrent use of any systemic or ocular tetracycline derivative (e.g. tetracycline, doxycycline, minocycline) at any dose is not allowed for the duration of the study.

ORACEA® can cause oral contraceptives to be less effective. Low dose oral contraceptives should not be used during the study unless with a second form of contraception.

Proton pump inhibitors, antacids or nutritional supplements containing aluminum, calcium, zinc, or magnesium and iron-containing preparations, including AREDS formula supplements, may impair ORACEA® absorption and should be taken at least 2 hours prior to or 3 hours after taking the study medication.

8. Concurrent Medical Conditions

All concurrent medical conditions (whether new or worsening) and present prior to or at the Baseline / Month 6 Visit (prior to initiating study drug) must be recorded in the Case Report Forms (CRFs) as concurrent medical conditions. All medical conditions, whether new or worsening and present after the initiation of the study drug at Month 6, must be recorded in the CRFs as adverse events, regardless of severity or assessed relationship to the study drug, and reported to the site’s Institutional Review Board (IRB) according to local site IRB guidelines. Collection of adverse events ends once the subject completes the End-of-Study Visit or Early Termination Visit (whichever occurs first). Refer to Section 14 for a description of adverse events and adverse event reporting requirements.

In the event the subject experiences a concurrent medical condition or adverse event (either new or worsening) during participation in the study, the subject may continue in the study with study drug treatment, unless the site investigator or Medical Monitor determines the subject should cease taking the study drug and/or be withdrawn from the study. A decision to withdraw a subject from the study should only be made after consulting with the Medical Monitor (as described in Section 12).

The clinical course of management of the concurrent medical condition should be recorded on the appropriate Case Report Forms (CRFs).

9. Conversion to Exudative Age-Related Macular Degeneration
9.1 “New” Exudative Age-Related Macular Degeneration

Subjects who develop new exudative ("wet") age-related macular degeneration in either the study eye or fellow eye during the Treatment Period will be instructed to immediately discontinue the study drug. In such cases, subjects will be asked to continue to complete all study follow-up visits and assessments.

9.2 Recurrent Age-Related Macular Degeneration

Subjects who develop recurrent exudative ("wet") age-related macular degeneration in the fellow eye during the Treatment Period will be allowed to continue on study drug. These subjects may receive treatment for their exudative AMD at the discretion of the site investigator.

10. Study Drug Administration

10.1 Study Drug

The study drug, ORACEA® (40 mg doxycycline) capsules are hard gelatin capsule shells filled with two types of doxycycline beads (30 mg immediate release and 10 mg delayed releases) that together provide a dose of 40 mg of anhydrous doxycycline. Galderma Laboratories, L.P. will supply the active drug (ORACEA®) and matching placebo comparator in identical 30 capsule bottles. The study drug bottles and drug kits will be packaged and labeled according to the randomization scheme. Packaged drug will be shipped to the Coordinating Center who will ship the drug to the sites.

The study drug will be dispensed to the subject with instructions for use. Subjects should take one (1) capsule each morning on an empty stomach (defined as at least one hour before or two hours after a meal). Administration of adequate amounts of fluid along with the capsules is recommended to wash down the capsule to reduce the risk of esophageal irritation and ulceration. The subject will continue with the once-daily (1 capsule) dosing for the duration of the 24-month Treatment Period.

In addition to initial distribution at following confirmation of eligibility criteria and study eye determination by the Boston Reading Center, study drug will be re-dispensed to subjects at the Month 6, 12, and 18 visits. Subjects should be instructed to bring their used and unused study drug to all study visits (scheduled
and unscheduled). At all study visits (scheduled and unscheduled) occurring after the initial distribution of the study drug, the Investigator or designated site personnel should assess the subject’s compliance with the study drug regimen (this will be done via capsule counting and recording). Used (empty) study drug bottles will be collected at Months 6, 12, and 18. All study drug bottles (used and unused) must be returned at the Month 24 (or Early Termination) visit.

10.2 Study Drug Storage

The site must store the study drug in a secure and safe area with limited or no access to individuals not involved in this study. The study drug should be stored at room temperature at 59°F to 86°F (15°C to 30°C) and out of light.

Subjects should be instructed to store the study drug in a secure and safe area that is out of reach to children. Subjects should be instructed that study drug should not be shared with anyone, including other study subjects. The subject should store the study drug at room temperature 59°F to 86°F (15°C to 30°C), in a tightly enclosed container (the study drug bottle is acceptable), and out of light.

10.3 Study Drug Accountability

The Site Investigator or designated site personnel must maintain accurate and complete records (including dates) of receipt of all study drug supplies. Drug accountability Case Report Forms must be completed by the Site Investigator or designated site personnel to document the dispensing and return of the study drug to subjects. Used (empty) bottles, partially-used (partially-empty) bottles, and unused (full) bottles of the study drug returned by the subject to the site should be maintained by the site (following the Study Drug Storage guidelines in Section 10.2) until all subjects have completed the study at the site. After all subjects have completed the study at the site, and approval is granted by the Coordinating Center, the site will be allowed to destroy the unused study drug according to their institutional / practice guidelines. A copy of the institution / practice guidelines or a Note to File outlining this procedure should be maintained in the site’s files.

10.4 Randomization and Study Drug Assignment

Study drug kits will be pre-labeled with a kit number corresponding to the randomization plan generated by the University of Virginia, Department of Public Health Sciences, Division of Biostatistics. Each subject drug kit will be assigned its own unique kit number and all study drug bottles in the kit will be individually labeled to correspond with the unique kit number and applicable bottle number.
The treatment assignments will be randomly assigned to the subjects. A permuted-block randomization scheme will be used to ensure approximate balance between treatment assignments (see Section 5.3.1 for details). Once a subject has been assigned a kit number, that kit and the bottles contained in that kit cannot be assigned to another subject.

10.5 Study Drug Masking

All subjects, all study personnel, and the Coordinating Center will remain masked to the study drug treatment assignments until the conclusion of the entire study (see Section 5.3.1 for details). Only the designated Biostatisticians (from the University of Virginia, Department of Public Health Sciences; Division of Biostatistics) will have access to the treatment assignments, but may not communicate the treatment assignments to any other study personnel at the Coordinating Center or at the remaining investigational sites, until conclusion of the entire study, and the central database has been officially locked.

In the rare event an emergency unmasking of a subject treatment assignment is required, the procedures outlined in Section 11 will be followed.

11. Emergency Unmasking of Subject Treatment Assignment

Emergency unmasking of an individual subject’s treatment assignment is only allowed in the rare case of a medical emergency where the Site Investigator (or Medical Monitor) believes the treatment assignment must be revealed to ensure subject safety.

In this situation, the Site Investigator should contact the study Medical Monitor to make a request to unmask the subject. The Medical Monitor will make the final decision as to if emergency unmasking is allowed. If the Medical Monitor approves the Site Investigator’s request to unmask the subject then the Site may proceed with unmasking.

If another situation arises in which the site investigator believes emergency unmasking is warranted, the situation must be discussed with the Medical Monitor and approval from the Medical Monitor is required prior to unmasking.

The subject’s treatment assignment will be revealed by one of the two Biostatisticians from the University of Virginia, Department of Public Health Sciences, Division of Biostatistics who have access to the randomization list. The treatment assignment should only be shared with individuals involved in the direct care of the subject who may require this information to make medical decisions and should not be shared with the Coordinating Center.
If the emergency unmasking of an individual subject’s treatment assignment occurs, the Site Investigator must document the purpose, date, and personnel involved in the unmasking (and communication of the treatment assignment information).

12. Subject Withdrawals and Subjects Lost to Follow-up

In the event a subject self-elects to discontinue the study drug or the Site Investigator (after consulting the Medical Monitor) elects to discontinue the study drug, every effort should be made by the Investigator and/or designated site personnel to encourage the subject to continue to complete all protocol required study visits and assessments and not withdraw from the study. However, a subject may withdraw from the study at any time.

12.1 Subject Withdrawals

All subjects will be advised via the written informed consent form and informed consent process that they have the right to withdraw from the study at any time or may be withdrawn at the discretion of the Study Investigator, Medical Monitor, or Coordinating Center. If a subject begins the Observation Phase and terminates the study prematurely (either by subject decision or Investigator, Medical Monitor, or Coordinating Center discretion), but prior to Randomization and starting study drug an Early Termination Visit is not required. Once a subject initiates the study drug and terminates the study prematurely (either by subject decision or Investigator, Medical Monitor, or Coordinating Center discretion), every effort should be made to complete an Early Termination Visit to evaluate the subject’s clinical status. For all subjects who terminate the study early, a reason for the subject’s early discontinuation should be documented on the appropriate Case Report Forms.

A subject may be withdrawn from the study for the following reasons:

- Subject withdraws consent
- The Site Investigator requests the subject is withdrawn
- The Medical Monitor or Coordinating Center requests the subject is withdrawn
- The subject’s primary care physician requests the subject is withdrawn
- Non-compliance with the study drug dosing schedule or study visit schedule
- Protocol deviation, protocol violation, or an unanticipated problem
- Lost to follow-up / failure to return for protocol visits
- Early Termination of the Study
- Worsening of another pre-existing disease
- Concurrent (new or worsening) medical condition that interferes with the use of the study drug or completion of the study assessments
- Clinical significant alteration / abnormality in laboratory values, physical exam, or ophthalmic exam after beginning the Observation Phase (Day 0 and beyond)

12.2 Subjects Lost to Follow-up

If a subject is lost to follow-up during the course of the study, the Site Investigator and/or designated study staff should make reasonable effort to contact the subject and at a minimum encourage the subject to return for an Early Termination Visit to evaluate the subject’s clinical status. All efforts to contact the subject should be documented in the source documents.

13. Rules for Termination of the Study

The study may be terminated at any time by the Sponsor. Reasons for terminating the study may include, but are not limited to:
- The incidence or severity of adverse events that indicate a potential health hazard to subjects
- Subject enrollment is unsatisfactory

14. Adverse Events

14.1 Adverse Event (AE) Definition

An adverse event is any sign, symptom, illness, or medical or psychological condition, not present prior to initiating the study drug, and which develops or worsens during the course of the study, whether or not the event is related to the study drug and whether or not the event is expected or unexpected. Medical conditions and diseases present prior to initiating study drug treatment will be considered adverse events only if they worsen after starting treatment with the study drug.

Some examples of adverse events are (but are not limited to):
- A change in the severity, frequency, or duration of a pre-existing condition
- Development of a new, concurrent medical condition
- Development of symptoms, which may or may not be related to the use of a concomitant medication or study drug, or concomitant surgical procedure.
• Laboratory result abnormalities or significant changes, but still within the site reference ranges, following initiation of treatment with the study drug, which the Investigator considers clinically significant.

14.2 Serious Adverse Event (SAE) Definition

A serious adverse event is any sign, symptom, illness, or medical or psychological condition, which results in any of the following outcomes:

• Death
• Is life-threatening
• Requires (≥ 24 hours) inpatient hospitalization or prolongs inpatient hospitalization
• Results in persistent or significant disability or incapacity
• Is a congenital anomaly or birth defect
• Is sight-threatening
• Is an important medical event - medically significant and which the Investigator regards as serious based on appropriate medical judgment

An adverse event is considered sight threatening and should be reported as a SAE if it meets one or more of the following criteria (for either the study or non-study eye):

• It causes a decrease of ≥ 30 letters in visual acuity (compared with the last visual acuity assessment), as assessed by ETDRS.
• It requires surgical intervention to prevent permanent loss of sight
• It is associated with severe intraocular inflammation (i.e. 4+ anterior chamber cell / flare or 4+ vitritis).
• In the opinion of the investigator, it may require medical or surgical intervention to prevent permanent loss of sight.

All Serious Adverse Events must be reported to the Coordinating Center within 24 hours of the site’s notification of the event; whether or not the Site Investigator believes the event is related to the study drug. All Serious Adverse Events must be reported to the site’s local IRB, in accordance with local regulations. If required, follow-up information should also be reported to the Coordinating Center and local site IRB in a timely manner. The Coordinating Center will then prepare the SAE for submission to the appropriate regulatory authorities within the required timeframe.

All Serious Adverse Events which are ongoing at the End-of-Study visit should be followed for an additional 30 days or until resolved, whichever occurs first.

14.3 Recording of Adverse Events (AEs) and Serious Adverse Events (SAEs)
All concurrent medical conditions (whether new or worsening) and present prior to or at the Day 0 / Screening Visit (prior to initiating study drug) must be recorded in the Case Report Forms (CRFs) as concurrent medical conditions. All medical conditions, whether new or worsening and present after the initiation of the study drug must be recorded in the CRFs as adverse events (and serious adverse events as indicated), regardless of severity or assessed relationship to the study drug, and reported to the site’s Institutional Review Board (IRB) according to local site IRB guidelines.

At all scheduled and unscheduled study visits, after initiation of the study drug the Investigator or designated personnel should record all voluntary complaints of the subject and directly question the subject regarding the occurrence of any adverse events since their last visit.

All adverse events (serious and not-serious), whether observed by the Investigator or Site Personnel, volunteered by or directly elicited from the subject, and regardless of the relationship with the study drug, should be recorded on the appropriate Case Report Form (the Adverse Event Log). The investigator or designated site personnel, should include a brief description of the adverse event, the date of onset, the date of resolution (when available, or marked as ongoing), the severity of the adverse event, the suspected cause of the adverse event, the possible relationship of the adverse event to the study drug, action taken with the study drug due to the adverse event, and the treatment for the adverse event. The assessment of the event severity and possible relationship to the study drug must be made by the Site Investigator or designee.

14.4 Adverse Event (AE) and Serious Adverse Event (SAE) Severity Definitions

The severity of each AE and SAE must be evaluated by the Site Investigator or designee and recorded, as one of the following on the Adverse Event Log:

- **Mild**: Transient (< 48 hours) or mild discomfort; no or minimal medical intervention / therapy required; no or limited interference with the subject’s daily activities.
- **Moderate**: Mild to moderate interference with the subject’s daily activities; possibly none, but usually minimal medical intervention / therapy required.
- **Severe**: Considerable interference with the subject’s daily activities; medical intervention / therapy required; hospitalization possible or likely.

14.5 Adverse Event (AE) and Serious Adverse Event (SAE) Relationship to Study Drug Definitions
For each AE and SAE, the relationship to the study drug must be evaluated by the Site Investigator or designee and recorded, as one of the following terms on the Adverse Event Log:

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>Clearly related to the study drug</td>
<td>The temporal relationship between the study drug exposure and the onset of the adverse event follows a reasonable sequence; follows a known response pattern to the study drug; and cannot be reasonably explained by the subject's current medical status or by other concomitant therapies / procedures.</td>
</tr>
<tr>
<td>Probably</td>
<td>Likely related to the study drug</td>
<td>The temporal relationship between the study drug exposure and the onset of the adverse event follows a reasonable sequence; follows a known response pattern to the study drug; and is unlikely to be explained by the subject's current medical status or by other concomitant therapies / procedures.</td>
</tr>
<tr>
<td>Possibly</td>
<td>May be related to the study drug</td>
<td>The temporal relationship between the study drug exposure and the onset of the adverse event follows a reasonable sequence; follows a known response pattern to the study drug; but may be reasonably explained by the subject's current medical status or by other concomitant therapies / procedures.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Likely not related to the study drug</td>
<td>The temporal relationship between the study drug exposure and the onset of the adverse event may follow a reasonable sequence; but the event may be able to be reasonably explained by the subject’s current medical status or by other concomitant therapies / procedures.</td>
</tr>
<tr>
<td>Unrelated</td>
<td>No possible relationship to the study drug</td>
<td>The temporal relationship between the study drug exposure and the onset of the adverse event does not follow a reasonable sequence, and/or the event is most likely explained by the subject’s current medical status or by other concomitant therapies / procedures.</td>
</tr>
</tbody>
</table>

**14.6 Adverse Event (AE) and Serious Adverse Event (SAE) Analysis**

All serious adverse events will be evaluated by the Medical Monitor.
The Data Safety Monitoring Committee (DSMC) will periodically review the masked adverse event and serious adverse event data.

14.7 Reportable Events

In addition to Serious Adverse Events, the following other events should be reported to the Coordinating Center within 24 hours of the site’s notification of the event and reported to the site’s Institutional Review Board (IRB) according to local site IRB guidelines:

- Subject withdrawal
- Premature discontinuation of the study drug
- Temporary suspension of the study drug
- Pregnancy
- Major Protocol Violation
- Other events, such as unanticipated problems, which the Site Investigator evaluates as requiring immediate reporting.

15. Data and Safety Monitoring Committee (DSMC)

An independent Data Safety Monitoring Committee (DSMC) has been appointed and is responsible for the periodic review and assessment of the study data, with a particular consideration of subject safety through the review of adverse events. The DSMC will meet at least every 6 months (with the first meeting to occur within 6 months of screening of the first subject) throughout the duration of the study, but may convene ad hoc meetings more frequently as required. In reviewing the accumulated study data, the DSMC will determine whether protocol modifications are necessary or if the study should continue without modifications. If the DSMC indicates changes in the protocol should be made, specific recommendations will be made to the Study Principal Investigator and Medical Monitor(s) for consideration and action as required. A report outlining the DSMC’s recommendations will be generated and disseminated after each meeting.

16. Statistical Analysis

16.1 Primary Objective and Endpoint

The primary study objective is to evaluate the efficacy of daily oral administration of ORACEA® compared with placebo control on the rate of change in the area of geographic atrophy (GA) as measured by fundus photography. The primary endpoint is the rate of change in the area of GA in the study eye during the Treatment Period of the study (Day 0 – Month 24).
16.1.1 Power Analysis

The information that was utilized in the power calculation comes from the article: “Change in Area of Geographic Atrophy in Age-Related Eye Disease Study” by Lindblad et al. in the Archives of Ophthalmology VOL 127(9) 1168:74 (2009) [33]. Lindblad et al. report that in 153 patients with GA, the average change in the area of GA from baseline was 3.78 mm$^2$ (SEM 0.24 mm$^2$) at two years, which corresponds to an average rate of change in the area of GA of 1.89 mm$^2$/year (SD 1.48 mm$^2$/year). They also report that in 181 participants with GA, the mean area of GA at baseline was 5.8 mm$^2$ (SEM 0.42 mm$^2$). Utilizing this information in the framework of Monte-Carlo simulation, we determined for a 30% difference in the yearly rate of change in the area of GA between ORACEA® and placebo control the relationship between sample size per study-group and the statistical power that we would have to reject the null hypothesis that ORACEA® administration for 2-years has no impact on the yearly average rate of change in the area of GA when compared to placebo.

16.1.2 Details

In the power calculations we assumed that the rate of change in the area of GA over the 2 year study period will be normally distributed within each of the two study populations (i.e. ORACEA® and placebo populations), and that the standard deviation (SD) of the distribution will be the same for the two study populations and that the SD will not exceed 1.48 mm$^2$/yr as reported by Lindblad et al [33]. We also assumed that the baseline area of GA and the yearly rate of change in the area of GA will be bivariate normally distributed with correlation coefficient $\rho$. All calculations of statistical power assume a two-sided type I error rate of 0.05 and each estimate for statistical power was derived based on the statistical tests of 1000 Monte-Carlo simulated ANCOVA models, with baseline area of GA as the covariate.

16.1.3 Power Simulation Results

Under the preceding set of assumptions, the statistical power to detect a 30% difference in the mean yearly rate of change in the area of GA between the ORACEA® group and the placebo group is presented in Table 1 as a function of sample size and the bivariate correlation ($\rho$) between the yearly rate of change in the area of GA and baseline area of GA. Note that under the most conservative assumption of 0 correlation between the yearly rate of change in the area of GA and the baseline area
of GA, the number of subjects required per study-group to achieve at least 0.80 statistical power is 107.

Table 1. Power to detect a 30% difference in the mean yearly rate of change in the area of GA between the ORACEA® group and the placebo group as a function of sample size and the bivariate correlation ($\rho$) between the yearly rate of change in the area of GA and the baseline area of GA.

<table>
<thead>
<tr>
<th>Sample Size/Group</th>
<th>0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.48</td>
<td>0.51</td>
<td>0.49</td>
<td>0.53</td>
<td>0.55</td>
<td>0.58</td>
<td>0.68</td>
<td>0.75</td>
<td>0.89</td>
<td>0.99</td>
</tr>
<tr>
<td>60</td>
<td>0.55</td>
<td>0.58</td>
<td>0.58</td>
<td>0.6</td>
<td>0.64</td>
<td>0.66</td>
<td>0.75</td>
<td>0.84</td>
<td>0.94</td>
<td>1.00</td>
</tr>
<tr>
<td>70</td>
<td>0.62</td>
<td>0.61</td>
<td>0.64</td>
<td>0.66</td>
<td>0.69</td>
<td>0.76</td>
<td>0.79</td>
<td>0.87</td>
<td>0.96</td>
<td>1.00</td>
</tr>
<tr>
<td>80</td>
<td>0.67</td>
<td>0.68</td>
<td>0.67</td>
<td>0.69</td>
<td>0.74</td>
<td>0.81</td>
<td>0.84</td>
<td>0.92</td>
<td>0.98</td>
<td>1.00</td>
</tr>
<tr>
<td>90</td>
<td>0.73</td>
<td>0.73</td>
<td>0.74</td>
<td>0.77</td>
<td>0.8</td>
<td>0.85</td>
<td>0.9</td>
<td>0.95</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>100</td>
<td>0.77</td>
<td>0.76</td>
<td>0.8</td>
<td>0.82</td>
<td>0.83</td>
<td>0.87</td>
<td>0.92</td>
<td>0.96</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>110</td>
<td>0.81</td>
<td>0.83</td>
<td>0.82</td>
<td>0.84</td>
<td>0.87</td>
<td>0.9</td>
<td>0.94</td>
<td>0.98</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

16.1.4 Subject Withdrawal

We anticipate based on similar age-related macular degeneration (AMD) studies that no more than 25% of the subjects who are determined to be eligible to participate and who are randomized to study drug (i.e. ORACEA® or placebo) at the Month 6 visit will fail to complete the entire 24-month treatment phase of the study protocol. Therefore, we intend to randomize a total of 286 subjects to the study drug. 143 will be randomized to ORACEA®, and the remaining 143 will randomized to placebo.

16.2 Primary Endpoint Analysis

The primary statistical analysis will be conducted in accordance with the guidelines of the intention to treat principle and will include all randomized subjects. The primary endpoint will be the rate of change in the area of GA in the
“study eye” during the Treatment Period of the study (i.e. Month 6 - Month 30). Random coefficient regression (RCR) will be utilized to estimate the marginal (i.e. population average) rates of change in the area of GA in the study eyes of subjects treated with ORACEA® and in the study eyes of subjects treated with the placebo. The response data for the RCR model will be the measurements of the area of GA at assessment months: 6, 12, 18 and 24. The primary RCR predictor variables will be the study-group (i.e. ORACEA® or placebo), and the exact number of days since the subject began the treatment phase of the study, divided by the average number of days per month (i.e. 29.604167 days). The RCR model will be specified so that the regression intercept coefficient and the regression coefficient associated with the variable “assessment time” (i.e. months of treatment) will be free to change depending on the study-group. Subject-specific measurements of the rate of the enlargement of the area of GA during the Observation Period will be utilized as covariate adjustment information in the RCR analysis. The RCR model fixed-effects and the RCR model random-effects will be estimated via restricted maximum likelihood. The random-effects will pertain to the RCR model intercept coefficient and the RCR model regression coefficient associated with the “assessment time” variable. Refer to Appendix F for the mathematical representation of the RCR model.

With regard to hypothesis testing, the primary null hypothesis will examine whether the marginal rate (i.e. mean population rate) of change in the area of GA in the study eye is the same regardless of whether the subject was treated with ORACEA® or treated with placebo, given that all eyes had the same average area of GA during the Observation Period of the study (i.e. covariate adjusted). A linear contrast of the “assessment time” regression coefficient estimates for the ORACEA® and placebo study-groups will be used as the pivotal quantity to test this hypothesis. The absolute value of the linear contrast will be compared to the 97.5 quantile value of the appropriate t-distribution. If the absolute value of the linear contrast is greater than or equal to the t-distribution 97.5 quantile value, the null hypothesis will be rejected. 95% confidence intervals will be constructed to estimate the covariate adjusted rate of change in the area of GA for eyes treated with ORACEA® and for eyes treated with placebo, as well as for the covariate adjusted mean difference in the rate of change in the area of GA between ORACEA® treated eyes and placebo treated eyes.

Model goodness of fit, will be evaluated via diagnostics of the Cholesky residuals. If deemed necessary, the area of GA data will be analyzed on an alternative scale of measure. Recent work by Feuer and colleagues [34] has shown that rescaling GA to a distance via the square root transformation produces GA time profiles that are more linear in nature as a function of assessment time.

The MIXED procedure of SAS version 9.2 (SAS Institute Inc., Cary, NC) will be used to conduct the RCR analysis.
16.3 Secondary Statistical Analyses

Several secondary endpoints will be analyzed (see Section 2.2.2), and all of the secondary statistical analyses will be conducted in accordance with the guidelines of the intention to treat principle and will include all randomized subjects.

16.3.1 Secondary Endpoint #1 Analysis

For subjects enrolled prior to this amendment, the change in the rate of enlargement in the area of GA in the study eye between the six month Observation Period (Day 0 – Month 6) and the 24 month Treatment Period (Month 6 – Month 30), as assessed by fundus photography and as assessed by fundus autofluorescence, will be analyzed by way of random coefficient piecewise regression (RCPR). The response data for the RCPR model will be the measurements of area of GA of the study eye during the observation phase and during the treatment phase of the study. The RCPR predictor variables will be the study group (i.e. ORACEA® or Placebo), and the exact number of days since the subject began the Observation Period of the study (Day 0), divided the average number of days per month (i.e. 29.604167 days). RCPR model will included a change point parameter that will allow the linear relationship between the response measurements (i.e. area of GA) and the “assessment” times to change abruptly at the start of the Treatment Period (Month 6 – Month 30), and by including the “study-group” by “assessment time” interaction terms in the RCPR regression model, the regression parameter estimates will be free to change from study-group to study-group.

With regard to hypothesis testing, based on the parameter estimates of the RCPR model, we will be able to test within both study-groups whether the rate of change in the area of GA in the study eye was on average the same during the Treatment Period and the Observation Period. We will also be able to test whether the rate of change in the area of GA in the study eye during any particular phase was study-group dependent. All of the hypothesis tests associated with the RCPR model will be based on linear contrasts of the RCPR model parameter estimates. The absolute value of each linear contrast will be compared to the 97.5 quantile value of the appropriate t-distribution. If the absolute value of the linear contrast is greater than or equal to the t-distribution 97.5 quantile value the null hypothesis will be rejected.

16.3.2 Secondary Endpoint #2 Analysis
The change in Best Corrected Visual Acuity (BCVA) as measured by ETDRS in the study eye at Month 24 as compare to Day 0 will be examined by way of analysis of covariance (ANCOVA). The change in ETDRS logMAR in the study eye from Day 0 to Month 24 will represent the response data for the ANCOVA model. Study-group (i.e. ORACEA® vs. Placebo) will represent the ANCOVA model independent factor, and ETDRS logMAR at Day 0 will represent the ANCOVA model adjustment variable (i.e. covariate).

With regard to hypothesis testing, we will test the null hypothesis that the mean change in ETDRS logMAR is the same regardless of whether the subject had been treated with ORACEA® or placebo, when both groups of subjects start out with the same ETDRS logMAR (i.e. covariate adjusted). A linear contrast of covariate adjusted means will be utilized to test the null hypothesis. The absolute value of the linear contrast will be compared to the 97.5 quantile value of the appropriate t-distribution. If the absolute value of the linear contrast is greater than or equal to the t-distribution 97.5 quantile value, the null hypothesis will be rejected.

16.3.3 Secondary Endpoint # 3 Analysis

The change in the composite NEI-VFQ 25 quality of life score from Day 0 to Month 24 will be examined by way of a negative binominal generalized estimating equation (GEE) model. The response data for the GEE model will be the composite NEI-VFQ 25 quality of life scores at Day 0 and at Month 24. The GEE model predictor variables will be the study-group (i.e. ORACEA® vs. Placebo) and the assessment time (Day 0 vs. Month 24).

With regard to hypothesis testing, we will use the GEE version of the Wald test to test the null hypothesis that the mean change in the composite NEI-VFQ 25 quality of life score from Day 0 to Month 24 is the same regardless of whether the subject is treated with ORACEA® or treated with placebo. A p≤0.05 decision rule will be utilized as the null hypothesis rejection criterion.

16.3.4 Secondary Endpoint # 4 Analysis

The proportion of ORACEA® treated subjects whose study eye progresses to exudative age-related macular degeneration by Month 24 will be compared to the proportion of placebo treated subjects whose study eye progresses to exudative age-related macular degeneration by Month 24. The endpoint analysis will be summarized on a binary scale. If by Month 24 the study eye has been clinically diagnosed as having exudative age-related macular degeneration, the binary outcome variable
will be assigned the value 1, if not, the binary outcome variable will be assigned the value 0. The binary data will be analyzed by way of exact logistic regression. Study-group (i.e. ORACEA® vs. Placebo) will represent the logistic regression predictor variable.

With regard to hypothesis testing, we will test the null hypothesis that the log-odds that the subject’s study eye progressing to exudative age-related macular degeneration by Month 24 is the same regardless of whether the subject was treated with ORACEA® or treated with placebo. A $p \leq 0.05$ decision rule will be utilized as the null hypothesis rejection criterion.

16.3.5 Secondary Endpoint # 5 Analysis

Utilizing the same statistical approach as just outline for the “Secondary Endpoint # 5” analysis, the proportion of ORACEA® treated subjects whose “fellow” eye progresses to exudative age-related macular degeneration by Month 24 in will be compared to the proportion of placebo treated subjects whose “fellow” eye progresses to exudative age-related macular degeneration by Month 30.

The MIXED, GENMOD, and LOGISTIC procedures of SAS version 9.2 (SAS Institute Inc., Cary, NC) will be used to conduct the secondary statistical analyses.

16.4 Exploratory Statistical Analyses

Several exploratory endpoints will be analyzed. Many of these endpoints will be measured in the subset of subjects who are enrolled at sites in which fundus autofluorescence and SD-OCT imaging is available. All of the exploratory statistical analyses will be conducted in accordance with the guidelines of the intention to treat principle and will include all randomized subjects.

16.4.1 Exploratory Endpoint # 1 Analysis

The rate of enlargement in the area of GA in the study eye during the 24-month Treatment Period (Day 0 – Month 24), as assessed by fundus autofluorescence, will be analyzed utilizing the same statistical approach as described in Section 16.2.

16.4.2 Exploratory Endpoint # 2 Analysis
For subjects enrolled prior to this amendment, the change in the rate of enlargement in the area of GA in the study eye between the six month Observation Period (Day 0 – Month 6), and the 24 month Treatment Period (Month 6 – Month 30) as assessed by fundus autofluorescence, will be analyzed utilizing the same statistical approach as described in Section 16.3.1

### 16.4.3 Exploratory Endpoint # 3 Analysis

The rate of enlargement in area of outer retinal disruption in the study eye during the 24-month Treatment Period (Day 0 – Month 24), as assessed by en-face spectral-domain optical coherence tomography (SD-OCT) of the inner segment / outer segment band will be analyzed utilizing the same statistical approach as in Section 16.2.

### 16.4.4 Exploratory Endpoint # 4 Analysis

Change in the rate of enlargement in area of outer segment disruption in the study eye between the six-month Observation Period (Day 0 – Month 6) and the 24-month Treatment Period (Month 6 – Month 30) as assessed by en-face spectral-domain optical coherence tomography (SD-OCT) of the inner segment / outer segment band, will be analyzed utilizing the same statistical approach as described in Section 16.3.1

### 16.4.5 Exploratory Endpoint # 5 Analysis

As a subgroup analysis on the rate of enlargement in area of geographic atrophy in the study eye during the 24-month Treatment Period (Month 6 – Month 30), as assessed by fundus photography, will be examined with subjects stratified into subgroups by baseline geographic atrophy size or rate of enlargement during the Observation Period (Day 0 – Month 6) to assess for treatment effect of ORACEA® within each subgroup. The analysis will be conducted utilizing the same statistical approach as described in Section 16.2.

### 16.5 Safety Data Analysis

Once the first subject has been randomized, closed and open Data Safety Monitoring reports will be generated at 6 month intervals. Adverse events (AEs) and serious adverse events (SAEs) will be summarized as frequencies and percentages by investigational site, and across investigational sites, for the open
report. For the closed report, AEs and SAEs will be summarized by investigational site, and across investigational sites, according to study arm.

Complete blood count with differential results, comprehensive metabolic panel results, and erythrocyte sedimentation rate results will be summarized by way of traditional summary statistics and by way of time trend summaries (slopes). For the open reports, the summaries will be computed by investigational site, and across investigational sites. For the closed report the summaries will be computed by investigational site, and across investigational sites, according to study arm.

In regard to statistical analyses, if the DSMC requests between study-group comparisons of AE and SAE frequencies, complete blood count with differential results, Comprehensive metabolic panel results, and erythrocyte sedimentation rate results, the comparisons will be provided. Otherwise, the safety data statistical analyses will be conducted via traditional statistical methods following study completion.

16.6 Missing Data

We anticipate that missing data will not be a frequent event, since the majority of the subjects who will participate in this study will receive similar tests and examinations as part of their standard of care. However, if a substantial number of data are missing, the multiple imputation methods of Rubin will be utilized [33]. The MI procedure of SAS version 9.2 (SAS Institute Inc., Cary, NC) will be utilized to impute missing data points, and to also facilitate performing the statistical analyses.

17. Regulatory and Ethics Requirements

17.1 Statement on Good Clinical Practice (GCP) Compliance

This study will be conducted in accordance with Good Clinical Practices (GCP) using the provisions set forth by the International Conference on Harmonization (ICH) and the United States Food and Drug Administration (FDA), and any applicable national and local regulations. This includes the applicable regulations under 21 Code of Federal Regulations (CFR).

17.2 Informed Consent

This study will be conducted in accordance with the provisions set forth by 21 CFR Part 50. The Coordinating Center must be given the opportunity to review the site’s informed consent form prior to site submission to the local IRB. The Coordinating Center must also be given the opportunity to review any modifications to the informed consent form or informed consent addendums.
issued by the site throughout the duration of the study, prior to site submission to the local IRB.

Informed consent is a process that is initiated prior to the subject’s agreement to participate in the study and continues through the subject’s study participation. IRB-approved informed consent forms will be provided to the subject and the subject will be asked to read and review the document. The informed consent form must be read and / or explained to each subject by the Investigator or designated site personnel. It is the Investigator’s responsibility to ensure the subject understands the informed consent form, all of the subject’s questions are answered, and that written informed consent form is obtained before the subject participates in any protocol required research procedures. The Investigator is responsible for maintaining the original signed informed consent form and providing the subject with a copy of the informed consent form.

17.3 Institutional Review Board (IRB) Review

The Sponsor and Coordinating Center will supply all necessary information and documents to the Investigator for submission of the protocol and informed consent form to the site’s local IRB. The Investigator is responsible for providing the appropriate materials to the IRB for review. A site may not begin the study until the appropriate local IRB approval(s) is received. A copy of the approval letter and approved consent form, as well as any other IRB approval documents must be submitted to the Coordinating Center prior to beginning the study.

The Coordinating Center will inform the Investigator of any protocol amendments or required modifications or addendums to the informed consent. The Investigator is responsible for informing the local IRB of any amendments to the protocol or informed consent form, and must obtain approval, when required prior to implementing. A copy of the approval letter and approved consent form must be submitted to the Coordinating Center.

The Site Investigator must ensure all subject recruitment materials are submitted to and approved by the site’s local IRB prior to use for subject recruitment. The Site Investigator is also responsible for reporting all adverse events, protocol deviations and violations, unanticipated problems, and DSMC Reports to the local IRB in accordance with local IRB guidelines.

The Site Investigator must obtain a list of their local IRB voting members responsible for reviewing the protocol. This list must be updated as necessary throughout the duration of the study. The Investigator is responsible for providing the local IRB with study progress reports in accordance with institutional and governmental regulations.
17.4 Protocol Amendments

Modifications to the protocol should only be made via a sponsor-issued protocol amendment. Each protocol amendment must be approved by the site’s local IRB prior to implementation at the site.

17.5 Subject Confidentiality

The Site Investigator is responsible for maintaining the privacy and confidentiality of subjects at all times, including complying with the obligations to research participants required by the Health Insurance Portability and Accountability Act (HIPAA). To help maintain privacy and confidentiality, subjects will be identified by code numbers on case report forms and other documents submitted to the Medical Monitor, Boston Reading Center, and the Coordinating Center and its delegates.

However, after the subject signs an informed consent, the site must permit authorized representatives of the Sponsor (this includes the Medical Monitor(s) and Coordinating Center) and federal and local regulatory agencies to review the signed informed consent form and all portions of the subject’s medical record that are directly relevant to the study.

17.6 Investigator Responsibilities

The Site Principal Investigator is responsible for the overall conduct of the study at the site. This includes maintenance of accurate and complete study records, such as source documents, case report forms, IRB records, adverse event records, sponsor correspondence, and regulatory documents. The study Manual of Operations will describe in detail the responsibilities of the Investigator and will provide a list of study documents that must be maintained.

17.7 Monitoring and Regulatory Inspections

This study will be monitored regularly by the Coordinating Center and the Coordinating Center’s authorized delegates. All individuals participating in monitoring activities are in compliance with Good Clinical Practices (GCP). The results of the site monitoring and study progress will be reviewed with the Investigator and other designated site personnel.
17.8 Data Management Responsibilities, Source Documents and Case Report Forms (CRFs)

Data collection is the responsibility of the site study personnel, under the supervision of the Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study. The Site must maintain primary source documents supporting all data entered on the Case Report Forms (CRFs). Source documents, include, but are not limited to: documentation of medical, surgical, and ophthalmic history; study visit record; laboratory results; documentation of telephone or electronic conversations with the subject; demographic information; original, signed informed consent form; records of hospitalization, non-study related procedures, or Emergency Department admissions; documentation of adverse events and changes in medication.

The study will utilize paper Case Report Forms (CRFs). The Sponsor / Coordinating Center will provide the CRFs to the site.

The University of Virginia will serve as the Coordinating Center for this study, and will be responsible for data management, quality review, analysis, and reporting of the study data.

17.9 Retention of Records

The Site Investigator is responsible for maintaining intact study records for a period of at least 6 years following the completion of the study. Study records may be retained for a longer period if required by local policies. Prior to disposing, changing location, or transferring custody of the study records, the Investigator should contact the Sponsor and/or Coordinating Center.
APPENDICES

APPENDIX A: Protocol Synopsis
APPENDIX B: Study Visit Schedule
APPENDIX C: References
APPENDIX D: NEI VFQ-25 Questionnaire
APPENDIX E: RCR Model, Mathematical Representation
APPENDIX A: Protocol Synopsis

<table>
<thead>
<tr>
<th>Protocol Title</th>
<th>A Randomized, Double Masked, Placebo Controlled Study Evaluating ORACEA® in Subjects with Geographic Atrophy Secondary to Non-Exudative Age-Related Macular Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Phase II / III</td>
</tr>
</tbody>
</table>
| Study Sites    | Investigational centers in the United States  
Coordinating Center – University of Virginia  
Statistical Center – University of Virginia |
| Study Drug     | ORACEA® (40mg doxycycline – 30mg Immediate Release & 10mg Delayed Release beads)  
ORACEA® or a matching placebo capsule will be taken once daily for 24 months. |
| Study Period   | Planned duration of study enrollment: 18 months  
Planned duration of Treatment Period (per subject): 24 months (Day 0 – Month 24)  
Planned duration of Study (per subject): 25 months |
| Study Population | 286 subjects, male and female and ≥ 55 years of age, with geographic atrophy in at least one eye (the study eye) due to non-exudative “dry” age-related macular degeneration.  
286 subjects (143 subjects per treatment group) will be randomized to either ORACEA® or matching placebo, to ensure approximately 214 subjects (107 per treatment group), complete the study. |
| Study Objectives | This study will assess efficacy and safety of daily oral administration of ORACEA® compared with daily oral administration of placebo comparator in subjects with geographic atrophy due to non-exudative age-related macular degeneration.  
The primary objective is to evaluate the efficacy of daily oral administration of ORACEA® compared with placebo control on the rate of change in area of geographic atrophy as measured by the change in area of geographic atrophy.  
The secondary objectives are to: evaluate the safety of daily oral administration of ORACEA® through the collection of adverse events and serious adverse events, vital signs measurement, and ocular and clinical laboratory assessments; and evaluate the efficacy of daily oral administration of ORACEA® with respect to visual acuity outcomes, anatomic outcomes, and subject-reported visual functioning outcomes. |
| Study Design   | This is a multicenter, randomized, double-masked, placebo controlled study. Subjects will be randomized in a 1:1 ratio to |
either ORACEA® or placebo, to be taken orally once-per-day for a period of 24 months.

This study consists of a Screening Visit (Day 0), followed by a 24-month Treatment Period, and followed by an End-of-Study Visit approximately 30 days after completion of the Month 30 visit.

After providing informed consent, potential subjects will undergo screening (Day 0) to determine if they are eligible to participate in the study. After eligibility is confirmed and the “study eye” is selected, subjects will be randomized in a 1:1 ratio to either the ORACEA® treatment group or placebo treatment group.

During the 24-month Treatment Period, subjects will return for follow-up study visits every 6 months at Months 6, 12, 18, and 24 (± 30 days). Site staff will be asked to contact the subjects via telephone at Months 3, 9, 15, and 21 (± 14 days). 30 days (± 7 days) after completion of the Month 24 visit, participants will be asked to return for an End-of-Study Follow-up Visit.

**KEY Inclusion Criteria**

1. Male or female, ≥ 55 years.
2. If a female of childbearing potential, must agree to use an effective form of contraception for the duration of the study and must have a negative serum pregnancy test at Day 0.
3. Willing and able to sign the informed consent.
4. Willing and able to return for all scheduled study visits and assessments and complete all study-related tests and procedures.
5. Best Corrected Visual Acuity (BCVA) of 20/20 – 20/400 in the study eye as measured by ETDRS.
6. Best Corrected Visual Acuity (BCVA) of hand motion or better in the non-study eye as measured by ETDRS.
7. Clinical diagnosis of geographic atrophy secondary to non-exudative age-related macular degeneration in at least one eye (study eye) as confirmed color fundus photography.
8. Geographic atrophy lesions of ≥ 0.75 and ≤ 7.0 MPS disc areas (≥ 1.995 mm² and ≤ 18.62 mm²) as measured by fundus photography in the study eye at Day 0.

**KEY Exclusion Criteria**

1. Geographic atrophy in the study eye due to causes other than non-exudative age-related macular degeneration.
2. History of or active presence of choroidal neovascularization secondary to exudative age-related macular degeneration in the study eye as confirmed by optical coherence tomography.
3. History of treatment or expected need for treatment in the study eye for the duration of the study with any anti-angiogenic therapy.
4. History of or active presence of choroidal neovascularization secondary to exudative age-related macular degeneration in the non-study eye requiring any treatment within 12 months (360 days) prior to Day 0 or expected to require treatment for the duration of the study.
5. Prior treatment for non-exudative age-related macular degeneration in either eye (excludes AREDS or other vitamin and mineral supplements).
6. Current or any previous history of treatment of the study eye with any tetracycline derivative for any ocular condition.
7. Active ocular inflammation (including trace or above) or active ocular or periocular infection within 90 days of Day 0 in the study eye.
8. Active presence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in the study eye.
9. Any history or active presence of severe dry eye disease, such as ocular rosacea, significant meibomian gland dysfunction, ocular herpetic infection, and sjogrens syndrome in the study eye.
11. Use of a tetracycline derivative therapy for a concurrent systemic or ocular disorder within 90 days of Day 0.
12. History of long-term (> 6 months within 5 years of Day 0) use of tetracycline therapy for a concurrent systemic or ocular disorder.
13. Laboratory tests indicating significantly impaired renal function (defined as eGFR less than 45 ml/min) or hepatic function (defined as ≥2x ULN).

**Study Endpoints**

The primary endpoint is the rate of enlargement in area of geographic atrophy in the study eye during the 24-month Treatment Period, as assessed by fundus photography. The secondary endpoints are: change in the rate of enlargement in area of geographic atrophy in the study eye between the six-month Observation Period (Day 0 – Month 6) and the 24-month Treatment Period (Month 6 – Month 30) as assessed by fundus photography; change in Best Corrected Visual Acuity (BCVA) as measured by ETDRS in the study eye at Month 24 as compared to Day 0; change in quality of life as measured by the NEI-VFQ25 at Month 24 as compared to Day 0; proportion of subjects progressing to exudative age-related macular degeneration in the study eye by Month 24 in the ORACEA® group as compared to the placebo group; proportion of subjects progressing to exudative age-related macular degeneration in the fellow eye by Month 24 in the ORACEA® group as compared to the placebo group.

The safety endpoints are: incidence and severity of ocular adverse
| events; incidence and severity of non-ocular adverse events; changes and abnormalities in clinical laboratory parameters; changes in vital signs. |
### APPENDIX B: Study Visit Schedule

<table>
<thead>
<tr>
<th>Test and Procedure</th>
<th>Screening / Day 0 (± 21 days)</th>
<th>Month 3 (± 14 days)</th>
<th>Month 6 (± 30 days)</th>
<th>Month 9 (± 14 days)</th>
<th>Month 12 (± 30 days)</th>
<th>Month 15 (± 14 days)</th>
<th>Month 18 (± 30 days)</th>
<th>Month 21 (± 14 days)</th>
<th>Month 24 (± 30 days)</th>
<th>End of Study (30 days ± 7 days)</th>
<th>Early Termination</th>
<th>Un-scheduled Visit</th>
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<tr>
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</tbody>
</table>

1. With the exception of Concomitant Medication Review, Adverse Event Review, and Study Drug Intake Review, all tests and exams to be performed at an Unscheduled Visit will be determined by the Investigator and are dependent upon the nature of the visit.

2. Optical Coherence Tomography (OCT) of both the study and fellow eyes is required at Screening / Day 0 and Month 24, but is optional at all other study visits and is dependent on if the site orders OCT as per standard practice.

3. Fundus Autofluorescence (FAF) is optional at all visits and is dependent on if the site orders FAF as per standard practice.

4. Laboratory Assessments include: Complete Blood Count with differential, Chemistry Profile, Erythrocyte Sedimentation Rate. In females of child-bearing potential a Serum Pregnancy Test is required at Screening / Day 0 and Urine Pregnancy Test at Months 6, 12, 18, 24, End of Study, and Early Termination Visits (and Unscheduled when applicable).

5. At Month 24 or the Early Termination Visit, all used (empty), partially used (partially empty), and unused (full) bottles of study drug should be collected.
APPENDIX C: References


APPENDIX D: NEI-VFQ 25 Questionnaire

PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the “National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

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7/28/96

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The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don't apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

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Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:
   (Circle One)
   Excellent................................ 1
   Very Good.............................. 2
   Good...................................... 3
   Fair...................................... 4
   Poor..................................... 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?
   (Circle One)
   Excellent............................... 1
   Good...................................... 2
   Fair...................................... 3
   Poor..................................... 4
   Very Poor............................... 5
   Completely Blind..................... 6

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3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time ......................... 1
A little of the time ...................... 2
Some of the time ...................... 3
Most of the time .................... 4
All of the time? ..................... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None.................................. 1
Mild.................................. 2
Moderate............................... 3
Severe, or ........................... 4
Very severe? ...................... 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all ............................. 1
A little difficulty ................................ 2
Moderate difficulty ......................... 3
Extreme difficulty ............................ 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ....................... 6

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6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

- No difficulty at all....................................................... 1
- A little difficulty............................................................. 2
- Moderate difficulty....................................................... 3
- Extreme difficulty......................................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this.................................6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

- No difficulty at all....................................................... 1
- A little difficulty............................................................. 2
- Moderate difficulty....................................................... 3
- Extreme difficulty......................................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this.................................6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

- No difficulty at all....................................................... 1
- A little difficulty............................................................. 2
- Moderate difficulty....................................................... 3
- Extreme difficulty......................................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this.................................6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

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10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

- No difficulty at all ........................................ 1
- A little difficulty ............................................ 2
- Moderate difficulty ......................................... 3
- Extreme difficulty .......................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ................................. 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

- No difficulty at all ........................................ 1
- A little difficulty ............................................ 2
- Moderate difficulty ......................................... 3
- Extreme difficulty .......................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ................................. 6
12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)
- No difficulty at all ......................................................... 1
- A little difficulty ......................................................... 2
- Moderate difficulty ..................................................... 3
- Extreme difficulty ....................................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ........................................ 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(Circle One)
- No difficulty at all ......................................................... 1
- A little difficulty ......................................................... 2
- Moderate difficulty ..................................................... 3
- Extreme difficulty ....................................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ........................................ 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)
- No difficulty at all ......................................................... 1
- A little difficulty ......................................................... 2
- Moderate difficulty ..................................................... 3
- Extreme difficulty ....................................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ........................................ 6

15. Are you currently driving, at least once in a while?

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15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Yes..................... 1 Skip To Q 15c
No ..................... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight.............................. 1 Skip To Part 3, Q 17
Mainly other reasons........................ 2 Skip To Part 3, Q 17
Both eyesight and other reasons .... 3 Skip To Part 3, Q 17

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all.......................... 1
A little difficulty............................ 2
Moderate difficulty......................... 3
Extreme difficulty........................... 4

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16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

- No difficulty at all .......................... 1
- A little difficulty ............................ 2
- Moderate difficulty .......................... 3
- Extreme difficulty ........................... 4
- Have you stopped doing this because of your eyesight ......................... 5
- Have you stopped doing this for other reasons or are you not interested in doing this ............................ 6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

- No difficulty at all .......................... 1
- A little difficulty ............................ 2
- Moderate difficulty .......................... 3
- Extreme difficulty ........................... 4
- Have you stopped doing this because of your eyesight ......................... 5
- Have you stopped doing this for other reasons or are you not interested in doing this ............................ 6

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PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

<table>
<thead>
<tr>
<th>READ CATEGORIES:</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Do you accomplish less than you would like because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. Are you limited in how long you can work or do other activities because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you’d like to be doing? Would you say:</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Not Sure</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. I stay home most of the time because of my eyesight.</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. I feel frustrated a lot of the time because of my eyesight.</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. I have much less control over what I do, because of my eyesight.</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Because of my eyesight, I have to rely too much on what other people tell me.</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. I need a lot of help from others because of my eyesight.</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. I worry about doing things that will embarrass myself or others, because of my eyesight.</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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APPENDIX E: RCR Model, Mathematical Representation

Random Coefficient Regression Model (Primary Analysis):

Eq 1. \( y_{ij} = \beta_0 + \beta_1 I_{1}^{(\text{ORACEA}^{(R)})} + b_{1i} + \beta_2 t_{ij} + \beta_3 I_{2}^{(\text{ORACEA}^{(R)})} \times t_{ij} + b_{2j} t_{ij} + \beta_4 \text{MGAOP}_i + e_{ij} \)

\[ i = 1, \cdots 286 \quad j = 1, \cdots, n_j \]

- \( y_{ij} \) denotes subject \( i \) geographic area (GA) at time \( j \).
- \( \beta_0, \cdots, \beta_4 \) denote the RCR model fixed regression parameters.
- \( b_{1i}, b_{2j} \) denote the RCR model subject-specific random effects associated with subject \( i \).
- \( e_{ij} \) denotes the residual error in the prediction of \( y_{ij} \).
- \( I_{1}^{(\text{ORACEA}^{(R)})} \) denotes an indicator function that equals 1 if subject \( i \) is randomized to the \( \text{ORACEA}^{(R)} \) and equals 0 otherwise.
- \( t_{ij} \) denotes the elapsed time (i.e. months) between subject \( i \) randomization and subject \( i \)\(^{th} \) GA measurement assessment during the intervention phase.
- \( \text{MGAOP}_i \) denotes subject \( i \) mean GA area during the observational phase.

Assumptions:
\[ \begin{bmatrix} b_{1i} \\ b_{2j} \end{bmatrix} \sim \text{iid } N \left( \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix} \right), \quad e_{ij} \sim \text{iid } N(0, \sigma^2). \]