Protocol Title: Evaluation of Oral Minocycline in the Treatment of Geographic Atrophy Associated with Age-Related Macular Degeneration

Abbreviated Title: GA MIN

Protocol Number: 15-EI-0202

Date of This Submission/Version: August 15, 2022/v13.0

Principal Investigator

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Principal Investigator – Biomedical Research Centre (BRC) Sites

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Coordinating Center: [redacted]

Participating Sites: [redacted]

Reading Center: [redacted]

Human Research Protections Program Investigator and Staff Training:

For this protocol, the following "Just in time" human subjects protection training courses are required for Investigators and staff: None

Total Requested Accrual:

60 Participants – 45 participants will be initially enrolled and included in the primary analysis – up to an additional 15 participants may be enrolled to account for participants who withdraw from the study before the Month 33 visit.

0 Healthy Volunteers

Project Uses Ionizing Radiation: ☒ No ☐ Yes

IND/IDE: ☐ No ☒ Yes
Drug/Device/#: 108,154
Sponsor: [redacted]

EUDRACT: ☐ No ☒ Yes
Drug/Device/#: 2017-000946-24
Sponsor: National Eye Institute

Durable Power of Attorney: ☒ No ☐ Yes

Multi-institutional Project: ☐ No ☒ Yes

Site	**FWA**
Coordinating Center: National Eye Institute (NEI)	FWA00005897
Participating Center: Bristol Eye Hospital (BEH) Principal Investigator:	FWA00000523 [redacted]

Additional sites may be identified and added to this study in future amendments.

Data and Safety Monitoring Board: ☐ No ☒ Yes

Technology Transfer Agreement: ☒ No ☐ Yes

Confidential Disclosure Agreement: ☒ No ☐ Yes

Samples Being Stored for Future Research: ☒ No ☐ Yes

Flesch-Kincaid Reading Level of Consent Form: 8.9

TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

TABLE OF CONTENTS (CONTINUED)

PROTOCOL ABBREVIATIONS LIST

AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
AMD	Age-Related Macular Degeneration
AREDS	Age-Related Eye Disease Study
BCVA	Best-Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CC	Clinical Center
CD	Clinical Director
CFH	Complement Factor H
CNS	Central Nervous System
CNV	Choroidal Neovascularization
CRIS	Clinical Research Information System
CTCAE	Common Terminology Criteria for Adverse Events
DIRRL	Doheny Image Reading & Research Lab
DSMC	Data and Safety Monitoring Committee
EDC	Electronic Data Capture
Emmes	The Emmes Company, LLC
EMR	Electronic Medical Record
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
EVA	Electronic Visual Acuity
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GA	Geographic Atrophy
ICRRC	Intramural Clinical Research Review Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board

PROTOCOL ABBREVIATIONS LIST (CONTINUED)

MI	Multiple Imputation
MPS DA	Macular Photocoagulation Study Disk Area
NEI	National Eye Institute
NGF	Nerve Growth Factor
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
OD	Oculus Dexter (Right Eye)
OS	Oculus Sinister (Left Eye)
PI	Principal Investigator
RPE	Retinal Pigment Epithelial
SAE	Serious Adverse Event
SNP	Single Nucleotide Polymorphism
SPF	Sun Protection Factor
TFT	Thyroid Function Test
USP	United States Pharmacopeia
UV	Ultraviolet
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
YAG	Yttrium Aluminum Garnet

PRÉCIS

Objective: Age-related macular degeneration (AMD), the leading cause of blindness in people over age 65 in the United States, is a heterogeneous clinical entity in which retinal degeneration occurs predominantly in the macula in the context of aging and leads to impairment of central visual acuity (VA). AMD occurs in two general forms, one of which involves choroidal neovascularization (CNV) with subsequent formation of a disciform scar. This is often referred to as the neovascular or "wet" form. A second form, the subject of this study, is termed "dry" /atrophic macular degeneration or otherwise "geographic atrophy" (GA) and involves a slow progressive atrophy of retinal pigment epithelial (RPE) cells and photoreceptors in the macula, also resulting in central vision loss. GA is estimated to affect up to one million persons in the U.S. and there is no current treatment that can prevent its onset or retard its progression. While the etiology of GA is not completely understood, inflammatory processes involving the activation of resident immune cells of the retina called microglia is likely to contribute. Minocycline inhibits the activation of microglia which produce inflammatory factors implicated in GA development. The objective of this study is to investigate the safety and possible efficacy of oral minocycline in patients with GA.

Study Population: Forty-five participants with unilateral or bilateral GA associated with AMD will be enrolled. However, up to an additional 15 participants may be enrolled to replace participants who may withdraw from the study prior to reaching the Month 33 visit.

Design: This is a multi-center, prospective, single-arm, Phase II study to evaluate minocycline as a potential treatment to decrease the rate of worsening of GA associated with AMD. Participants will undergo a nine-month run-in phase prior to receiving investigational product (IP). During this run-in phase, participants will have a total of four pre-treatment visits. Following the run-in phase, beginning at Month 9, participants will receive an oral dose of 100 mg of minocycline twice daily for 36 months (i.e., through Month 45). There will be a common termination date, which will take place when the last recruited participant has received 36 months of treatment. Participants who were recruited in the earlier part of the study will continue treatment and be followed every six months until the common termination date. However, participants may complete participation in the study as early as Month 45, at the discretion of the investigator.

Outcome Measures: The primary outcome is the rate of change in area of GA based on grading by an external Reading Center of fundus autofluorescence (FAF) images in the assigned study eye. The primary outcome will compare the rates of GA area expansion as determined on FAF images before and following the initiation of IP until 24 months of treatment. Secondary outcomes will compare differences in rates of change in best-corrected visual acuity (BCVA), low-luminance VA, area of GA based on FAF (using a different statistical approach compared to primary outcome) and fundus photography. The exploratory outcome will compare the difference in the rate of change in macular sensitivity as measured using microperimetry. This outcome was originally a secondary outcome when the clinical trial participants were enrolled, since these represent visual function data corresponding closely to areas affected by geographic atrophy. Hence, changes in microperimetry data over time might be well placed to support changes in structural data over time, as geographic atrophy lesions undergo enlargement. In the original Statistical Analysis Plan, the intention was that "Macular sensitivity, as measured on microperimetry, will be evaluated in a similar manner as BCVA", (i.e., "Mean rate of change in BCVA during the treatment phase will be compared to the mean rate of change in BCVA during the run-in phase using Student's paired t-test"). However, microperimetry data (represented by multiple numerical values, one for each anatomical location, at each time-point) are much more complex than BCVA data (represented by a single numerical value at each time-point). The originally proposed statistical treatment is therefore not suitable. In addition, the study team is not aware of any established methods accepted by the community for analyzing microperimetry data, unlike the situation for BCVA. Indeed, the microperimetry acquisition pattern used in GA MIN is unique and was developed specifically for this trial. It therefore needs its own dedicated set of statistical analyses (which may need several iterations), rather than pre-specified and widely accepted analyses that could be detailed in advance in the Statistical Analysis Plan. For these reasons, although the original intention was for the microperimetry data to represent a secondary outcome measure, it is better suited to an exploratory outcome measure. Safety outcomes will include the number and severity of adverse events (AEs). Ocular safety outcomes will be indicated by changes in VA, ocular surface changes, intraocular inflammation and any other ocular changes not consistent with the natural progression of GA.

1.0 INTRODUCTION

1.1 Age-related Macular Degeneration

AMD is the leading cause of late onset visual impairment and legal blindness in people 65 years of age or older in the United States (1, 2). The World Health Organization has placed AMD as the third leading cause of blindness worldwide. The phrase "age-related" is associated with macular degeneration because data show that the risk of developing AMD dramatically increases after age 60. It is estimated that 13 million people in the U.S., age 40 and older, have signs and symptoms of macular degeneration. Based on population demographics and current prevalence data, the number of individuals affected with AMD will double in the year 2020.

AMD is a disease of the macula, the central area within the posterior retina that helps produce sharp, central vision. Central vision is required for seeing objects clearly and for common daily activities essential for independent living such as reading, writing, sewing and driving. While the pathogenesis of AMD remains unknown, several lines of evidence have indicated the role of inflammation. Complement factor H (CFH) is a major regulatory factor in the complement cascade. Several groups have identified single nucleotide polymorphisms (SNPs) in the CFH gene that are associated with AMD. A single copy of the risk-associated haplotype increases the risk of AMD by two- to four-fold, whereas those with a dual copy may increase their lifetime risk by five- to seven-fold (3-7). Macrophages are known to have an important role in the initiation and maintenance of the immune response, including the regulation of complement activation. Previous studies have shown that patients with AMD were more likely to have circulating, activated macrophages (which produce high amounts of proinflammatory cytokines) compared to controls without AMD (8).

1.2 Treatment of Age-related Macular Degeneration

Treatment of AMD has mostly focused on therapy for neovascular AMD. These have included classic laser photocoagulation, photodynamic therapy (verteporfin, Visudyne®) and anti-vascular endothelial growth factor (VEGF) pegylated aptamer (pegaptanib sodium, Macugen®), an anti-VEGF monoclonal antibodies ranibizumab (Lucentis®) and aflibercept.

In October 2001, the results of the Age-Related Eye Disease Study (AREDS), a multi-center, randomized, controlled clinical trial of high-dose vitamins C and E, beta carotene and zinc supplements demonstrated a 25% reduction in the risk of progression to late AMD (9). However, this effect appears to be limited to reducing risk for progressing to neovascular AMD and does not influence the risk for progression to GA (unpublished data).

There are currently no available treatments or therapies for GA that have demonstrated efficacy in either preventing the onset, slowing the progression of disease, or improving vision of affected patients.

1.3 Geographic Atrophy

Atrophic AMD or GA is characterized by an absence of neovascular changes and the gradual progression of atrophic changes in the macula on the level of outer retina and the RPE cell layer, resulting in progressive central vision loss. Over time, this progresses to result in serious impairment of central vision and often legal blindness. Wet or exudative AMD can also arise in the context of GA. Both GA involving the center of the macula and wet AMD are considered forms of late AMD.

One of the most common signs in early or intermediate AMD is drusen, which is typically seen in people over the age of 60. Drusen are usually seen clinically as whitish-yellow irregularities under the retina. Large drusen have been shown to contain immunoglobulins, activated microglia and fragments of activated complement factors (10-12), which may be a source of chronic inflammatory stimulus in the aging retina. In the absence of findings consistent with late AMD, intermediate AMD is typically defined as the presence of large (>125µm) macular drusen and/or pigmentary (hypopigmentary or hyperpigmentary) changes, while early AMD is typically defined as the presence of macular drusen < 125µm in size.

2.0 SCIENTIFIC RATIONALE FOR USE OF ORAL MINOCYCLINE IN THE TREATMENT OF GA

2.1 Microglial Involvement in the Inflammatory Etiology of AMD

While the etiology of AMD is not completely understood, chronic neuroinflammation in the retina is thought to play an important causative role (13). Genetic analyses have implicated immune molecules, particularly those in the complement system, in conferring risk for AMD (14-16). Drusen, the hallmark of early and intermediate AMD, contain complement molecules (11, 17), as well as oxidation products from lipid and carbohydrates that can initiate inflammatory and immune responses (18, 19).

Microglia are the primary resident immune cells in the retina and are implicated in the response and propagation of relevant pathological inflammatory processes in AMD (13). Activated microglia and macrophages have been found in the outer retina of AMD eyes (20, 21) and in close proximity to GA lesions (22). In mouse models of AMD, outer retinal accumulations of activated microglia are prominent and associated with late AMD lesions. Activated microglia in the outer retina appear capable of inducing cellular changes in the outer retina that characterize GA, such as the loss in RPE integrity and regularity (23), as well as photoreceptor cell death (24). Inhibition of microglia/macrophage recruitment to the outer retina in mouse models decreases photoreceptor degeneration in AMD-related animal models, further implicating their causal role (25). As a result, inhibition of microglial activation may be a promising therapeutic approach in AMD (26) in limiting the production of pro-inflammatory mediators in the outer retina and arresting/retarding progressive RPE and photoreceptor degeneration in GA.

2.2 Minocycline as an Inhibitor of Microglial Activation: Preclinical Studies

Minocycline is a member of the tetracycline family of antibiotics that in addition to its antimicrobial properties acts as an anti-inflammatory agent and an inhibitor of microglial activation (27, 28). Minocycline can exert its anti-inflammatory effects on microglia in culture, inhibiting proliferation and release of proinflammatory mediators (IL-1β, IL-6, TNF-α, NO), and promoting production of nerve growth factor (NGF), leading to decreased inflammatory cell death and increased neuroprotection (29-31). Minocycline crosses the blood-Central Nervous System (CNS) barrier readily, providing high bioavailability in the CNS; as a result, it has been evaluated

as a therapy in a number of animal disease models where microglial-mediated neuroinflammation features. In a mouse model of diabetic retinopathy, systemic minocycline decreased inflammatory cytokine production, reduced the release of cytotoxins from activated microglia, and lowered the rate of apoptosis in the retina (32). In a mouse model of subretinal hemorrhage, intraperitoneally-administered minocycline reduced microglial infiltration into the outer retina and delayed consequent photoreceptor atrophy (33). In mouse models of retinal degeneration in which pro-inflammatory cytokine production and microglial activation occur (34-38), systemic minocycline was found effective in slowing down the rate of photoreceptor cell death (39, 40).

2.3 Minocycline: Clinical Use and Clinical Studies

Minocycline is FDA-approved for treating infectious disorders and is indicated for the treatment of various gram-positive and -negative bacteria. In ophthalmology, oral minocycline is commonly used for the treatment of blepharitis and ocular rosacea (41). It has a favorable side-effect profile, although it should not be used in pregnancy as the use of tetracycline class of drugs during tooth development may cause permanent tooth discoloration.

Oral minocycline is used widely and has been shown to be well tolerated when used at the FDA-approved doses. A study comparing the AEs reported with the number of prescriptions for minocycline for the years 1998 to 2003 estimated the rate to be 13 reported AEs per million prescriptions per year (42). The majority of these events were gastrointestinal upset, photosensitivity, hyperpigmentation, and tooth discoloration.

Minocycline has also been used in clinical trials as an inhibitor of microglial activation. In a clinical trial of acute stroke, 74 patients treated with oral minocycline (200 mg) for five days demonstrated a significantly better neurological outcome compared with 77 patients on placebo (43). Minocycline is currently being investigated in ongoing clinical studies to decrease symptom progression in Huntington's disease (NCT00277355), and to provide neuroprotection in Parkinson's disease (NCT00063193) and amyotrophic lateral sclerosis (ALS) (NCT00047723). In the area of retinal diseases, a pilot, proof-of-concept study of diabetic macular edema reported an association between oral minocycline administration and improved visual function, retinal edema, and vascular leakage (NCT01120899) (44).

3.0 STUDY OBJECTIVE

The primary objective of this study is to investigate the safety and possible efficacy of oral minocycline for slowing down the worsening of GA associated with AMD.

4.0 PARTICIPANTS

Forty-five participants, ages 55 years and older, with unilateral or bilateral GA associated with atrophic AMD will be initially accrued. Approximately 20-25 participants will be enrolled at NEI, and approximately 20-25 participants will be enrolled at BEH to reach the target sample size of 45 participants. Participants who withdraw or are lost to follow-up before the termination of enrollment at all sites may be replaced by new enrollments up to 30 participants at NEI and 30 participants at BEH. Listed below are the inclusion and exclusion criteria.

4.1 Participant Eligibility Criteria

4.1.1 Inclusion Criteria

To be eligible, the following inclusion criteria must be met, where applicable:

1. Participant must be 55 years of age or older.
2. Participant must understand and sign the protocol's informed consent document.
3. Participant must have evidence of early or intermediate AMD as defined by characteristic presence of drusen and/or pigmentary changes.
4. Participant must be able to swallow capsules.
5. Participant must have normal renal function and liver function or have mild abnormalities not above grade 1 as defined by the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).
6. Participant must agree to minimize exposure to sunlight or artificial ultraviolet (UV) rays and to wear protective clothing, sunglasses and sunscreen (minimum sun protection factor (SPF) 15) if s/he must be out in the sun.

7. Any female participant of childbearing potential (see Appendix 1 for definition) must have a negative pregnancy test at screening and be willing to undergo pregnancy tests throughout the study.
8. Any female participant of childbearing potential (see Appendix 1 for definition) and any male participant able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, be completely abstinent* from intercourse or must agree to practice two acceptable methods of contraception throughout the course of the study and for at least one week after investigational product (IP) discontinuation. Acceptable methods of contraception include:
    a. hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring),
    b. intrauterine device,
    c. barrier methods (diaphragm, condom) with spermicide, or,
    d. surgical sterilization (hysterectomy or tubal ligation).

    *Abstinence is only acceptable when it is the participant's preferred and usual lifestyle choice. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

A participant is not eligible if any of the following exclusion criteria are present.

1. Participant is actively receiving study therapy in another investigational study.
2. Any female participant of childbearing potential (see Appendix 1 for definition) that is pregnant, breast-feeding or planning to become pregnant during the study.
3. Participant is expected to be unable to comply with study procedures or follow-up visits.
4. Participant is on ocular or systemic medications known to be toxic to the lens, retina or optic nerve (e.g., ethambutol, chloroquine, or hydroxychloroquine).
5. Participant has a condition that would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control) by interfering with the participant's ability to engage in the required protocol evaluation and testing and/or comply with study visits.

6. Participant has a history of chronic renal failure requiring dialysis or kidney transplant.
7. Participant has a history of chronic hepatitis or liver failure.
8. Participant has a history of thyroid cancer.
9. Participant has an allergy or hypersensitivity to minocycline or any drug in the tetracycline family.
10. Participant is currently taking minocycline or another tetracycline medication.
11. Participant is taking any medication that could adversely interact with minocycline such as methoxyflurane.
12. Participant has a prior history of idiopathic intracranial hypertension.

4.2 Study Eye Eligibility Criteria

The participant must have at least one eye meeting all inclusion criteria and none of the exclusion criteria listed below.

4.2.1 Study Eye Inclusion Criteria

1. The study eye must have greater than ½ disc area (approximately 1 mm^2) of GA compatible with dry AMD. GA is defined as one or more well-defined and often circular patches of partial or complete depigmentation of the RPE, typically with exposure of underlying choroidal blood vessels. Even if much of the RPE appears to be preserved and large choroidal vessels are not visible, a round patch of RPE partial depigmentation may be classified as early GA. The GA in the study eye must be able to be photographed in their entirety, and it must not be contiguous with any areas of peripapillary atrophy, which can complicate area measurements.
2. The total area of GA lesions combined should be less than 7.0 Macular Photocoagulation Study (MPS) disc areas (DA) (17.78 mm^2) as evident on FAF imaging.
3. The VA of the study eye should be ≥19 Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) letters (i.e., 20/400 or better).

4. The study eye must have clarity of ocular media and degree of pupil dilation sufficient to permit adequate fundus photographs.

4.2.2 Study Eye Exclusion Criteria

1. Current evidence of choroidal neovascularization (CNV) as determined by the treating physician or a history of treatments for CNV.
2. Evidence of retinal atrophy due to causes other than atrophic AMD.
3. Current evidence or history of ocular disorders in the study eye that in the opinion of the investigator confounds study outcome measures, including (but not limited to):
    a. non-proliferative diabetic retinopathy involving 10 or more hemorrhages or microaneurysms, or active proliferative diabetic retinopathy,
    b. Branch or central retinal vein or artery occlusion,
    c. Macular hole,
    d. Pathologic myopia,
    e. Uveitis,
    f. Pseudovitelliform maculopathy.
4. History of vitreoretinal surgery.
5. Need for ocular surgery during the course of the study.
6. Recent history of lens removal (< three months) or Yttrium Aluminum Garnet (YAG) laser capsulotomy (< one month).

4.2.3 Choice of Study Eye in Cases of Bilateral Disease

If both eyes meet the study eye eligibility criteria described above, the eye with the better BCVA will be chosen as the study eye. If both eyes are of equal VA, the study eye will be assigned by the enrolling investigator. For participants with two qualifying eyes, the fellow (non-study) eye will be noted as a “qualifying fellow eye” and anatomical data from it will be analyzed as part of the secondary outcome measures.

5.0 STUDY DESIGN AND METHODS

5.1 Study Overview

This is a multi-center, prospective, single-arm, Phase II clinical trial of up to 45 participants with GA associated with AMD. The amended study design relies on the linearity of the GA expansion rate in the natural history of the disease in a single eye using the square root transformation of the GA area. The linearity of GA expansion rate over the time scales relevant to the study were verified in exploratory analyses on two previous GA studies Othera (NEI Protocol 06-EI-0116) and SIRGA (NEI Protocol 09-EI-0008).

Participants will undergo a nine-month run-in period prior to receiving IP. Starting at Month 9 (IP start visit), participants will receive 100 mg minocycline orally twice a day for a total of at least 36 months (i.e., through Month 45). All participants will be followed for a minimum of 45 months over 11 or more study visits. There will be a common termination date, which will take place on or after the date when the last-recruited participant has received 36 months of IP, although some participants may complete participation in the study as early as Month 45, at the discretion of the investigator. As GA is a slow, progressive, retinal disease involving the gradual expansion of the area of atrophy on a time-scale of square microns per month, every effort will be made to retain participants for the entire duration of the study.

5.2 Recruitment

Forty-five participants will be initially enrolled in this study. However, up to an additional 15 participants may be enrolled to replace participants who may withdraw prior to reaching the Month 33 visit.

Approximately 20-25 participants will be recruited from the NEI clinic, and most of the participants for this study can be recruited from the current patient population with GA and AMD at the NEI retina clinic. The study will also rely on referrals from physicians at Kaiser Permanente and other local eye clinics. A recruitment flyer will be posted at community gathering places including but not limited to: hospitals, libraries, senior centers, senior housing facilities, area metro and bus stops, websites, newspapers and throughout the NIH campus. Recruitment materials such as letters to physicians and potential participants will be used. It is anticipated that all participants will be recruited within 12 months.

Approximately 20-25 participants will be recruited from the BEH site. Participants from this site will be identified following attendance at routine outpatient appointments or sent a recruitment letter from existing databases of patients diagnosed with GA and AMD and who routinely attend the BEH site for treatment.

It is anticipated that all participants will be recruited within 12 months. The recruitment totals are not fixed at each site. No more than 30 participants will be enrolled at either the NEI or UK site.

5.3 Screening

Consent will be obtained before any study procedures are done, including any screening procedures that may be done under this current protocol. At the NEI clinic, all potential participants will undergo a screening visit in the NEI ophthalmology clinic to determine whether they meet the eligibility criteria. Potential participants will be screened under protocols such as the NEI screening protocol (NIH Protocol 08-EI-0102), AREDS follow-up protocol (NIH Protocol 08-EI-0043), Biobank protocol (NIH Protocol 12-EI-0042), or DA AMD protocol (NIH Protocol 11-EI-0147) to establish eligibility. Each potential participant must have an active signed consent for one of the above-mentioned protocols on file in order to allow for screening examination. The following tests are performed during the screening protocols and may be used for the initial study visit for the current protocol if they are performed within the specified time frames:

1. Stereoscopic color fundus photography, FAF and infrared reflectance imaging, microperimetry, and OCT performed within 30 days prior to the initial study visit.
2. Physical examination (including thyroid palpation), acute care panel, hepatic panel, complete blood count (CBC) and thyroid function test (TFT) performed within 60 days prior to the initial study visit.

Evaluations previously performed outside of the windows indicated above may be used to determine participant eligibility, and these evaluations will be repeated under this study at the initial study visit. At any time during the screening process, the participant may enroll in this current protocol by signing the protocol's consent form and may complete any remaining screening and baseline procedures under this protocol, with final determination of eligibility. Women of childbearing potential (see Appendix 1 for definition) must have a negative test within 24 hours

prior to initiation of investigational product. If BCVA, manifest refraction, low-luminance visual acuity, slit lamp examination, and/or intraocular pressure (IOP) were assessed on an earlier date under another protocol, these will be repeated as initial study visit examinations on the day of enrollment. If a participant is unable to complete microperimetry testing, the microperimetry testing may be waived for subsequent study visits and the investigator will specify the reason the test could not be completed. All other screening procedures will not be repeated. These screening/initial study visit examinations are outlined in Appendix 2. The enrolling Investigator will confirm that all eligibility criteria have been met. If determined eligible, the participant will sign the informed consent and enroll at his/her initial study visit.

At the BEH site, all potential participants will only be screened under this study protocol.

5.4 Study Design

This study will examine the effect of oral minocycline in participants with GA in at least one eye that is associated with AMD. Participants will undergo a nine-month run-in period prior to receiving IP. During the run-in period, participants will return to the clinic at Months 3, 6 and 9 for ocular assessments. Starting at Month 9, participants will receive 100 mg minocycline orally twice a day from the IP start visit until study termination. Participants will return to the clinic at Months 12, 15 and every six months thereafter. The study is designed with a common termination date, meaning it will not terminate until the last recruited participant has completed the Month 45 visit. Therefore, participants enrolled at the beginning of the study could receive additional months of IP beyond the scheduled 36 months. However, participants may complete participation in the study as early as Month 45, at the discretion of the investigator. Although participants may withdraw from IP during the study, all participants will be asked to return for all visits through their study termination visit.

5.5 Study Procedures

The study will require a minimum of 11 visits (Months 0, 3, 6, 9, 12, 15, 21, 27, 33, 39 and 45). All visits must be conducted within a window of ± 30 days. It is anticipated that the study duration will not exceed 57 months if all participants are recruited within the first 12 months. At or prior to the IP start visit, the participant will undergo a complete vital sign assessment and a complete

review of systems. Comprehensive ophthalmologic examinations and safety assessments will be performed as outlined in the study flowsheet (Appendix 2).

If participants are on anticoagulation at enrollment, they must visit their prescribing physician to check their anticoagulation status within two-four weeks after initiating IP to have their anticoagulation regimen adjusted if necessary (as taking minocycline may require an increase of anticoagulation medication dose).

Participant compliance with study IP administration will be prompted through ongoing encouragements and reminders during study visits and scheduled and unscheduled telephone contacts. Compliance will be assessed by capsule counts conducted during study visits. Overall compliance rate based on previous long-term studies in AMD with twice daily dosing is expected to be fairly good (about five out of six participants took >75% of the study IP) (50c). Occurrences in which the computed compliance rate between study visits falls below 50% will be reported as a protocol deviation.

5.6 Ocular and Systemic Evaluations

Over the course of the study, participants will undergo the following ocular and systemic evaluations as outlined in the study flowsheet (see Appendix 2):

1. Medical/Ophthalmic History
2. Concomitant Medications Assessment
3. Vital Signs
4. Physical Examination
5. Adverse Event Assessment
6. Best-corrected visual acuity (BCVA)
7. Manifest Refraction using Electronic Visual Acuity (EVA) tester
8. Low-luminance visual acuity (VA) testing (study and qualifying fellow eye(s)) [5]
9. Intraocular Pressure (IOP)

10. Slit Lamp Examination
11. Dilated Fundus Examination
12. Measurement of retinal sensitivity using microperimetry (mesopic for study eye(s) and scotopic for qualifying fellow eye(s))
13. Color Fundus Photography
14. Fundus Autofluorescence (FAF) Imaging
15. Infrared Reflectance Imaging
16. Optical Coherence Tomography (OCT)
17. Fluorescein Angiography (FA)[4]
18. Acute Care Panel[1]
19. Hepatic Panel[1]
20. Complete Blood Count (CBC)
21. Thyroid Function Test (TFT)[1,2]
22. Thyroid Palpation[3]
23. Pregnancy Test for Females of Childbearing Potential[1] (See Appendix 1 for definition)

[1] All clinically significant abnormal values or positive tests will be reported to the participant's primary care physician, with the participant's permission.

[2] Clinically significant abnormal TFT results that emerge during the course of the study will lead to referral to an endocrinologist.

[3] Clinically significant abnormal findings during a thyroid palpation that emerge during the course of the study will be followed by a referral to an endocrinologist.

[4] Throughout the study, investigators will review retinal images to definitively ascertain the absence of CNV. If the absence of CNV cannot be definitively ascertained based on retinal images at the Month 9 visit, FA will be performed. If positive for CNV, the participant will be discontinued from the study if they have only one eligible study eye but may continue in the study if the fellow eye is eligible.

[5] Evaluations on non-qualifying fellow eyes may be performed for routine clinical evaluation for the continuing care of the participant as determined by the treating investigator.

It is expected that these tests can be completed in one clinic visit over one day. Physical examination performed within 60 days of study enrollment may be admissible for the initial study visit evaluation. In the event that the testing was not completed within a day, subsequent clinic visits may be scheduled within 10 days of the first visit to complete the scheduled evaluation. The frequency of the tests, however, varies depending on the visit. The schedule for each test is outlined in the study flowsheet (Appendix 2).

5.7 Study and Concomitant Therapies

5.7.1 Formulation of Minocycline at NEI

At the NEI site, minocycline hydrochloride capsules for oral administration containing the equivalent of 100 mg of minocycline will be investigated under Investigational New Drug (IND) Number 108,154.

5.7.2 Formulation of Minocycline at BEH

At the BEH site, minocycline hydrochloride capsules for oral administration containing the equivalent of 100 mg of minocycline will be investigated under European Clinical Trials Database.

5.8 Dosage, Administration and Storage

Adult participants will be instructed to take their prescribed IP orally two times a day, once in the morning and once in the evening, approximately 12 hours apart. The capsules will be dispensed to the participant in a tight, light-resistant container as defined in the United States Pharmacopeia (USP) in three-month supply aliquots. Starting at Month 9 and continuing at Month 12, a three-month supply will be dispensed to the participant during the study visit or mailed to the participant. Participants will be given an instruction sheet for taking the prescribed IP (Appendix 4). Starting at Month 15 participants will receive two bottles for a six-month supply. The IP should be stored between 15-30°C (or 59-86°F). They should be protected from light, moisture, and excessive heat. Participants will be required to bring their bottles of IP to each appropriate visit for capsule counts for compliance monitoring.

5.9 Concomitant Therapy

The use of periocular and intraocular corticosteroids is not permitted in study eyes or qualifying fellow eyes. The use of anti-VEGF agents is not permitted in study eyes or qualifying fellow eyes.

Participants will be instructed not to take minocycline or other tetracycline-class antibiotics for any other reason during the study. Participants should avoid taking penicillin while in this study.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and preparations that include iron. Participants will be instructed to wait two hours after taking their IP before taking one of these antacids.

Participants must not receive methoxyflurane for the duration of the study.

Review of concomitant medications will be conducted with participants at each study visit after initiation of IP and recorded.

5.10 Investigational Product Accountability

The indicated pharmacy for each site is responsible for the accountability of all dispensed and returned IP. Adequate drug accountability records include documentation of all IP shipped, received, dispensed and returned to the indicated pharmacy. The investigator is responsible for the accountability of all dispensed IP at their respective site. Adequate drug accountability records include documentation of all IP prescribed by the Investigators. Returned IP will be collected and stored by each pharmacy in a secure location until reconciliation by the Coordinating Center. Following reconciliation by the Coordinating Center, each pharmacy will dispose of returned IP.

5.11 Follow-up/Termination Procedures

At the conclusion of the study, participants will no longer be eligible to receive IP under this protocol.

At NEI, follow-up care will be arranged with either an outside ophthalmologist or the participant will continue to be seen at the NIH under another protocol if available and if the participant is eligible. The participant and his/her physician will be informed of the participant's disease status during this study. Clinical data obtained during participation will be shared with participants and, with written permission from the participants, their private physicians. Results from the overall study will be listed on http://www.clinicaltrials.gov once the data have been analyzed.

If a participant terminates from the study between study visits, the assessments to be conducted at this termination visit will be at the discretion of the investigator.

5.12 Storage of Samples and Data

No samples will be stored for this study. At the NEI site, the clinical data will be stored in the NEI's electronic medical record (EMR), clinical research information system (CRIS) and The Emmes Company, LLC database. At the BEH site, the clinical data will be stored in The Emmes Company, LLC's database.

6.0 RISKS/DISCOMFORTS

The anticipated discomforts and inconveniences of this protocol are those associated with the IP, the diagnostic procedures, and the time required for the participant to spend at the clinic.

6.1 Examination Risks

There are risks associated with the procedures required for participants in this study. Some of the discomforts associated with the ocular examination include the following:

1. Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause an infection, but neither of these problems is very likely to occur. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available. The participant's intraocular pressure will be obtained at each ophthalmic examination to determine whether there is an increased risk of developing glaucoma.
2. Stereoscopic color fundus photographs involve a bright flash to take pictures of the retina. This brief flash may cause temporary discomfort, but it does not damage the eye.
3. OCT and microperimetry are non-invasive tests used to document and analyze retinal pathology and have minimal medical risks.
4. The fluorescein dye used in FA can make a participant's skin turn yellow for several hours. This yellow color is transient and usually disappears in one day. Because the dye undergoes renal excretion, the participant's urine will turn dark orange for up to 24 hours after the

examination. The study team will educate the participant regarding this urine color change. Some participants may be slightly nauseated during the examination, but their nausea usually lasts only a few seconds. If the dye extravasates during the injection, the skin around the injection site may feel mildly uncomfortable or become yellow. The discomfort usually lasts only a few minutes, and the yellow color fades in a few days. There is a chance of ecchymosis at the site of injection and a remote possibility of cellulitis from the needle track. In rare cases, participants may have an allergic reaction to the dye. Treatment typically consists of an oral antihistamine medication but may require intravenous antihistamine administration if the symptoms are severe. Very rarely (less than one in one million people), a participant experiences anaphylaxis. This would be treated immediately by trained personnel with medications or, if necessary, intubation.

Possible discomforts associated with non-ocular examinations include:

1. Blood draws can cause discomfort and bleeding/bruising at the site of venous puncture. There is a remote risk of fainting or local infection. If any of these conditions arise, they will be treated.
2. The medical/ophthalmic history, vital signs, review of systems and pregnancy testing entail minimal medical risk.

6.1.1 Risks Associated with Minocycline

Risks associated with minocycline are largely associated with oral dosing at a typical dose of 100mg twice daily. The following adverse reactions have been observed in patients receiving typical oral doses of tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial over growth) in anogenital region and increases in liver enzymes. Rarely, hepatitis and liver failure have been reported. Rare instances of esophagitis and esophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed.

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions, including balanitis, have been rarely reported. Erythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported with minocycline. Pigmentation of the skin and mucous membranes has been reported.

Renal toxicity: Elevations in blood urea nitrogen (BUN) have been reported and are apparently dose related. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the IP and possible liver toxicity.

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and rarely pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome has also been reported.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

Central Nervous System: Central nervous side effects including light-headedness, dizziness, or vertigo have been reported with minocycline therapy. Headache and blurred vision have also been reported. Serious neurologic events reported include bulging fontanels in infants and benign intracranial hypertension (Pseudotumor cerebri) in adults.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. Very rare cases of abnormal thyroid function have been reported. Thyroid cancer has been reported in the post-marketing setting in association with minocycline products, although the incidence is presently unknown. The internal medicine consult service will perform thyroid palpation for Visit 000 and will communicate the results to the Investigators. The study investigators will perform the same thyroid palpation as outlined in the study flowsheet (Appendix 2). Any clinically significant abnormalities on thyroid

palpation and/or thyroid function test (TFT) will prompt a referral to an endocrinologist. Decreased hearing has been rarely reported in patients on minocycline hydrochloride. Tooth discoloration in children less than eight years of age and, rarely, in adults has been reported. Use is not recommended for individuals of either gender attempting child conception. There is a risk of impaired spermatogenesis. Because tetracycline can reduce the amount of beneficial forms of bacteria in the body, participants will be counseled to include probiotics in their diet while participating in the study.

Pregnant and Nursing Women: Minocycline is in Pregnancy Category D and is excreted in human milk. Minocycline can cause fetal harm when administered to a pregnant woman. The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of eight years) may cause permanent discoloration of the teeth (yellow-grey-brown).

6.1.2 Drug Interaction-related

Because tetracyclines have been shown to depress plasma prothrombin activity, participants who are on warfarin (Coumadin) may require downward adjustment of their anticoagulant dosage. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and also preparations that include iron. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. Concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.

7.0 PARTICIPANT SAFETY MONITORING

Participants will be assessed during each study visit after initiation of IP for AEs by the study Investigators. At each visit after initiation of IP, the participant will be asked about any new ocular or systemic symptoms including rashes, hospitalizations or new/changed medications. General and ophthalmic assessments will be performed according to Appendix 2. Stopping guidelines for individual participants and the entire study are outlined below.

7.1 Participant Withdrawal Criteria

Participation in the study is strictly voluntary. Participants may choose to withdraw from this study for any reason at any time without penalty, without loss of benefits or prohibition from enrolling in other clinical protocols. All participants will be included in the analyses at the end of the study.

The investigator may withdraw a participant at their discretion for the following reasons:

- Investigator determination that it is not in the best medical interest of the participant to continue participation;
- Findings in the course of the trial that may affect willingness to participate;
- The development of AMD-related CNV in the study eye of the participant;
- Participant requires additional medicines or subconjunctival or intravitreal injections that will interfere with the IP;
- Pregnancy;
- Serious suspected adverse reaction;
- VA loss of >30 letters from initial study visit;
- Any other safety concerns;
- Inability to keep study visits or to comply with study requirements.

Discontinuation of IP does not require participant withdrawal from the protocol. If the participant agrees to continue in the study after discontinuing IP, s/he will continue to return for their subsequent study visits and undergo the required examinations. Otherwise, the participant will exit the study and continue his/her ophthalmic care either with an outside ophthalmologist or at the NEI. Participants will be monitored by study Investigators and clinical staff at each visit to the clinic.

7.2 Pregnancy Monitoring

If an investigator becomes aware that a female study participant has become pregnant during the study, the investigator will advise the participant to stop taking the IP immediately. The investigator and participant will determine whether to continue any remaining study visits or to exit the study.

If an investigator becomes aware that a male study participant has impregnated his partner during the study, the investigator will remind the participant of the potential risks to the unborn fetus.

In either case of reported pregnancy, the participant (and/or partner) will be referred to the NIH OB/GYN consultation service for evaluation and counseling. The investigator must follow the participant (or partner) through the pregnancy outcome. The data must be recorded on the *Confirmed Pregnancy and Outcome* form in the Electronic Medical Record (EMR), which is also reported to the Coordinating Center.

8.0 OUTCOME MEASURES

8.1 Primary Outcome

The primary outcome is the difference in the rates of GA area expansion in the study eye between the run-in phase of the study and following IP initiation. GA area determination will be based on digital grading of FAF images by an external Reading Center. The primary outcome will be the difference in the rate of GA area expansion from IP start visit (Month 9) to 24 months of treatment (Month 33) compared to initial study visit (Month 0) to IP start visit.

8.2 Secondary Outcomes

Secondary outcomes will examine the differences in the rates of outcome measure progression in the study eyes between the run-in phase of the study and following IP initiation. These outcome measures include: GA area expansion based on FAF images by an external Reading Center using a different statistical approach compared to primary outcome, GA area expansion based on digital grading of color fundus images by an external Reading Center, changes in BCVA, changes in low luminance VA, changes in central retinal thickness on OCT. Measures obtained from qualifying fellow eyes (i.e., fellow eyes of participants that also meet eye-specific eligibility criteria) will also be analyzed separately and together with study eyes as secondary outcome measures.

8.3 Exploratory Outcome

The exploratory outcome will compare the difference in the rate of change in macular sensitivity as measured using microperimetry. This outcome was originally a secondary outcome when the clinical trial participants were enrolled, since these represent visual function data corresponding

closely to areas affected by geographic atrophy. Hence, changes in microperimetry data over time might be well placed to support changes in structural data over time, as geographic atrophy lesions undergo enlargement. In the original Statistical Analysis Plan, the intention was that "Macular sensitivity, as measured on microperimetry, will be evaluated in a similar manner as BCVA", (i.e., "Mean rate of change in BCVA during the treatment phase will be compared to the mean rate of change in BCVA during the run-in phase using Student's paired t-test"). However, microperimetry data (represented by multiple numerical values, one for each anatomical location, at each time-point) are much more complex than BCVA data (represented by a single numerical value at each time-point). The originally proposed statistical treatment is therefore not suitable. In addition, the study team is not aware of any established methods accepted by the community for analyzing microperimetry data, unlike the situation for BCVA. Indeed, the microperimetry acquisition pattern used in GA MIN is unique and was developed specifically for this trial. It therefore needs its own dedicated set of statistical analyses (which may need several iterations), rather than pre-specified and widely accepted analyses that could be detailed in advance in the Statistical Analysis Plan. For these reasons, although the original intention was for the microperimetry data to represent a secondary outcome measure, it is better suited as an exploratory outcome measure.

8.4 Ocular Safety Outcomes

Ocular safety outcomes will be indicated by changes in VA, ocular surface changes, intraocular inflammation and any other ocular changes not consistent with the natural progression of GA.

9.0 STATISTICAL ANALYSIS

All participants will be followed throughout the duration of the study and included in the analyses.

9.1 Study Design and Primary Analysis

Rate of change in GA, based on digital grading of FAF, will be monitored throughout the study period in both the study and fellow eyes. A spline regression model with a fixed knot at Month 9 will be computed to compare the rates of change in GA from IP start visit to 24 months of treatment and from initial study visit to IP start visit in the study eyes of all participants (49). Spline regression is a linear modeling method used to assess the longitudinal effects of an

intervention on an outcome of interest (49). Splines require at least one break in the study time period, a knot. This knot represents a specific point in time that is hypothesized to be the starting point of change from the previous, established trend (49), (50).

The spline regression model will compute the slopes for the run-in period and for the treatment period. This method will allow for the comparison of the two slopes and will test whether the slopes are significantly different (50). A square-root transformation will be used in an attempt to satisfy the linear trend assumption of the spline regression model (Box-Cox or logarithm transformations may also be attempted if a square-root transformation does not achieve a sufficient linear trend). Ninety-five percent confidence intervals for the rate of change and difference in rates will also be calculated–based on the transformed data and back transformed to the rate scale.

9.2 Handling Data Irregularities

Although the study will make efforts to ensure maximum participant compliance, data irregularities, including protocol deviations, noncompliance, withdrawals, missing values and losses to follow-up, may occur and will impact the proposed analyses. These analyses will be conducted on all participants enrolled in the study, regardless of compliance, follow-up or treatment received. Since the primary outcome is a rate of change, all available FAF data from participants who discontinue from the study prior to their Month 9 or 33 study visit will be modeled with a longitudinal within-participant linear regression model. This model will determine each participant's annualized rate of progression (i.e., slope of regression line for FAF area over time).

Sensitivity of the data based on the above population to missing observations will be assessed by comparing the results with Multiple Imputation (MI) analysis and the treatment-received analysis based on the Per Protocol (PP) population (without missing observations). In the MI analysis, participants' post-treatment data will be utilized in a longitudinal regression model to estimate annualized rate of progression. This analysis assumes that GA progression rates are similar pre and post-study withdrawal. In the MI analysis, MI method will be used to generate many different annualized progression rates for participants who withdraw early. More specifically, the MI procedure will 1) generate multiple imputed datasets (approximately 2,000); 2) perform a t-test for each dataset; and 3) finally combine t-values with standard errors that reflect the uncertainty

inherent in imputation. Under the assumption that the transformation of the rates of change in area of GA are normally distributed, the missing rates from the run-in phase and the treatment phase will be predicted from each participant's observed area of GA, and scheduled visits and joint relationships with other variables (e.g. participant's age, visual acuities, OCT measurements).

The final analysis for the longitudinal data throughout the follow-up will treat missing observations completely at random (MCAR).

Participants' compliance with IP administration will be assessed through capsule counts during study visits. If study IP compliance falls below 80% of the level prescribed for any participant, the participant will be queried about the reasons for decreased compliance and counseled on the importance of compliance for study integrity. The level of compliance will be reported to the IRB on annual review and taken into account in the analyses of study outcomes. To ensure the study is not biased by IP noncompliance, statistical analyses will look at the associations between IP compliance, dropout, and treatment effect during Months 12, 15, and 21. If IP compliance cannot be determined for a participant during any visit, IP compliance will be imputed by taking the median of all capsule counts recorded at previous study visits.

9.3 Analysis of Secondary Endpoints

Any participant who completes three or more visits during the treatment phase will be included in these analyses.

VA will be evaluated in both the study and fellow eyes at each scheduled visit, with the secondary outcome defined as a three-line worsening in BCVA. A change from initial study visit of 15 letters score (three lines) or more, is considered clinically significant. Mean change in BCVA during the treatment phase will be compared to the run-in phase.

Development of wet AMD as measured by OCT will be monitored throughout the study period in both the study and fellow eyes. Absolute and relative changes in GA will be assessed using fundus photography and FAF imaging throughout the study period.

Safety outcomes, including the number and severity of AEs will be tabulated by severity, type and assessed relatedness to the IP. The number of participants withdrawn from the IP due to vision loss, AEs and treatment failure will also be tabulated.

These analyses will be descriptive and will include tabulations of outcomes over the study period. Some nonparametric analyses may be utilized for exploratory analyses of secondary endpoints.

9.4 Sample Size/Accrual Rate

The accrual goal is to enroll 45 participants, approximately 20 at NEI and 25 at BEH. This sample size was determined for the primary analysis of the difference in rate of change in square-root transformed GA area in the study eye between IP start visit to 24 months of treatment and initial study visit to IP start visit. A two-sided paired t-test at an alpha level of 0.05, comparing square-root transformed rates of change in GA between 24 months of treatment and the run-in phase was employed.

A rate of 1.52 mm^2/year is assumed for the run-in phase in the current study, based on the median GA expansion rates suggested in the literature (45). For data that are skewed, the square-root of the mean is not equal to the mean of the square-root transformed data. However, since a quantile of strictly positive data is invariant to transformation (e.g., the square-root of a given quantile of the original observations is equal to that quantile of the transformed observations), and for symmetric data mean and median are equal, the square-root of the median progression rate ($\sqrt{1.52}$ mm^2/year = 1.23 mm/year) is used to approximate the assumed mean progression rate for the square-root transformed run-in phase. The treatment phase is assumed to have a 25% reduction in the GA growth rate, equivalent to a 13% reduction of the square-root transformed rate, implying a mean progression rate of 1.07 mm/year for the square-root transformed GA growth rate during the treatment phase. A standard deviation of 0.30 mm/year was obtained from previous NEI GA protocols exploratory analyses data and was assumed for the GA growth rate during the run-in phase. Given the strictly positive nature of GA enlargement, a reduction in mean progression rate during the treatment phase necessitates a smaller standard deviation. However, on the square-root scale, the difference in standard deviations between the run-in and treatment phases is negligible for the proposed 25% reduction in means, and a standard deviation of 0.30 was also assumed for

the square-root transformed GA growth rate during the treatment phase. Since this is a single arm study utilizing each participant as their own control, measurements will be highly correlated between the run-in and treatment phases. A correlation of 0.8 was used to account for the high dependence in measurements between the run-in and treatment phases. Since the study population consists of older adults, loss to follow-up due to various reasons is expected and needs to be taken into account for an accurate sample size. Based on these square-root transformed mean and standard deviation estimates, a sample size of at least 17 participants is required to obtain at least 90% power to detect a difference in progression rates if the true square-root transformed progression rates are 1.23 mm/year during the run-in phase and 1.07 mm/year during the treatment phase of 24 months, with an 80% within-in participant correlation. Approximately 12 months will be necessary to accrue these participants. After the first 15 participants have reached their Month 9 visit, the study dropout rate will be assessed and a sample size re-estimation may be performed.

Sunness, et al. (46), (45) state that a sample size of 306 is necessary to detect a treatment effect of 25% when examining the effect of a new systemic treatment on GA growth rate in individuals (46). One of the factors that resulted in the reduction of sample size from the Sunness suggestion is the use of FAF instead of CFP to grade GA. FAF appears to be more precise (i.e., lower within-patient SD) than CFP. For example, the coefficient of variation for the square-root transformed FAF data is 2.5, while the coefficient of variation for the CFP data summarized in Sunness is 1.3. Further, the current study design utilizes each participant as their own control, significantly decreasing within-participant variability and the need for a large sample size.

10.0 HUMAN PARTICIPANTS PROTECTION

10.1 Equitability

Accrual will be equitable for this study. Minimum age of participation was set at 55 years as GA in the context AMD does not typically occur in patients younger than this age; including patients < 55 years old will increase the risk of enrolling “masqueraders” (i.e., patients with clinical findings similar to GA but arise from a different etiology).

10.1.1 Justification for Exclusion of Children

Children will not be eligible for this study, as the condition under study affects primarily adults.

10.1.2 Justification for Exclusion of Pregnant or Lactating Women

Pregnant or lactating women are not eligible for this study because of the known and unknown risks of minocycline. One of the known risks of minocycline is that it can cause permanent discoloration of the teeth (yellow-grey-brown) of a fetus when given to a pregnant woman during the last half of pregnancy. Minocycline also passes into breast milk and can cause permanent discoloration of the teeth of a nursing infant. Given the known and unknown effects on pregnancy outcomes, two forms of contraception will be required for female participants of childbearing potential (see Appendix 1 for definition). In addition, female participants of childbearing potential will undergo urine pregnancy tests throughout the study.

10.1.3 Refraction and Visual Acuity

Specific certification in EVA techniques for refraction and visual acuity determinations is required for this study. Certification involves a practicum and testing in the competent use of the technique and the proper recording of the data. Each person (e.g., physician, optometry professional, ophthalmic technician and/or nurse) that performs these determinations on study participants must be certified. If necessary, training and certification in the EVA methods can be provided prior to study initiation. The Coordinating Center must review and approve any training or certifications not conducted by Emmes staff. Emmes may grandfather existing certifications if candidates are currently certified for similar procedures in other NEI studies and have been actively performing the EVA refraction and visual acuity testing protocol.

10.1.4 Photography Qualification

DIRRL will qualify the site to perform OCT, FAF, color fundus photography, and microperimety imaging as specified in the DIRRL Study Instruction Manual.

10.1.5 Professional Licensure

Physicians must provide evidence of current medical licensure applicable to the study location(s) if they are practicing medicine and undertake to diagnose and/or treat participants (including administration of the investigational product) in this study. A physician who is a site PI must also provide satisfactory evidence of ophthalmology training before study initiation.

11.0 ANTICIPATED BENEFIT

Participants may benefit directly from this study if study drug decreases the progression of GA and preserves VA. The study will also lead to generalizable knowledge that will enhance our understanding of using minocycline as treatment for participants with GA associated with AMD.

12.0 CONSENT DOCUMENTS AND PROCESS

Study Investigators with consenting privileges will obtain informed consent. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study. The participants must have the ability to understand and sign an informed consent form, which must be signed prior to enrollment. The participants will have an opportunity to carefully review the consent and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves. If the participant requires the consent to be in larger font in order to read it well, this will be provided. If participants are visually impaired to the point of being unable to read the consent, they can take the consent back with them to read it over with a family member or with the use of magnifying devices. If the participant chooses, the investigator can also read the consent verbatim to the participant and answer any questions that may arise.

An investigator present during the consent process will document the consent process in the participant's medical record. A copy of the signed informed consent form will be provided to the participant to take home.

13.0 DATA AND SAFETY MONITORING

The PI and the NEI DSMC are responsible for monitoring data and safety and will exercise oversight of the clinical investigation independently from the study Investigators.

13.1 Coordinating Center

Emmes has been assigned as the Coordinating Center for this trial to conduct data collection, protocol monitoring, data analysis and reporting. The Coordinating Center provides routine monitoring of study participants' data. Monitoring visits will occur on a schedule depending on the status of the study. More frequent monitoring visits will be performed at the beginning of the study when enrollment is open. Monitoring will decrease as enrollment closes and as participant follow-up continues.

Communications between the investigational site and the Coordinating Center will be maintained through regular telephone and e-mail contacts between the Coordinating Center Protocol Monitor and the site PI and/or Coordinator. Substantive communications must be maintained both at the site and at the Coordinating Center containing the date and a summary of communications where instructions are given or received, an interpretation of protocol requirements is made, recommendations for corrections to study documentation are made, or where the reporting of possible AEs is discussed.

Although the Coordinating Center advises the NEI Clinical Director (CD) and PI on data and statistical activities, the Coordinating Center staff does not have direct access to or interaction with participants.

13.2 Data and Safety Monitoring Committee

The NEI DSMC is responsible for reviewing and approving the study design and, as appropriate, recommending design changes. In addition, the DSMC assesses study data with particular consideration of participant safety. The DSMC will convene prior to the initiation of the trial to review the protocol. Emmes will provide accumulated data from all study sites to the NEI DSMC. The Committee will review accumulated data at minimum twice a year but will convene ad hoc meetings to address any significant problems related to participant safety brought to its attention by any study participant or investigator. The Committee will review the accumulated data and consider whether a protocol modification is necessary and approve protocol modifications. If changes in protocol are indicated, recommendations will be made to the NEI Director and CC Director who will consider and act on such recommendations in a timely manner.

13.3 Criteria for Stopping the Study

The DSMC may recommend temporarily suspending or closing enrollment or stopping the study at any time due to safety concerns, demonstration of efficacy or lack of efficacy, or slow recruitment.

14.0 QUALITY ASSURANCE

The NEI and Emmes maintain quality control by adhering to standard operating procedures (NEI QA program and NEIS standard operating procedures). These procedures cover the full protocol cycle beginning with staff credentialing and training, and protocol development and approval, through database development, data collection, monitoring and analysis, and finally manuscript preparation at the conclusion of the study. Data quality assurance is of the utmost importance to the NEI and Emmes. The two groups use a quality assurance system that relies on real-time data checks and reports throughout the course of a study to ensure the accuracy of information. This system is a secure and confidential data management system that stores data and provides quality assurance and reporting. Emmes has developed a number of routine reports specifically designed for monitors (e.g., listings of serious adverse events (SAEs), etc.).

Additionally, Emmes has developed summary reports of discrepancies, as well as reports of the exceptions databases, which include requests and reasons for exceptions. The results of the reports are communicated back to site staff, and, along with protocol compliance issues, to the DSMC (if applicable).

Following the monitoring plan for this study, Emmes will perform monitoring activities, including on-site audits, review of database entries and the resolution of study issues. Per the monitoring plan, the frequency of interim monitoring visits is every six months from enrollment through the end of participant follow-up. Site visit frequency modifications may be made to accommodate increases or decreases in the quantity of data requiring review and as deemed necessary by the Sponsor and coordinating center, with the minimum site monitoring frequency to occur no less than annually. In addition to monitoring, Emmes performs various detailed automated and manual data quality checks on an ongoing basis. The results from these checks and any protocol compliance issues are communicated back to site staff and to the NEI Project Officer, NEI CD and applicable regulatory bodies.

15.0 REPORTABLE EVENTS

Reportable events will be tracked and submitted to the IRB as outlined in Policy 801.

16.0 ALTERNATIVES TO PARTICIPATION

High-dose vitamin supplementation can reduce the progression to exudative AMD (12). Participants will be allowed to take AREDS-type vitamin supplements during the course of the trial. Currently, there are no other treatments which have been approved for the treatment of GA in AMD. Therefore, participants do not forego any known effective treatments and the alternative is not to participate in the study. Participants can alternatively receive minocycline outside of the study if prescribed off-label by their own physician.

17.0 PRIVACY

All research activities will be conducted in as private a setting as possible.

18.0 CONFIDENTIALITY

No blood, tissue or other samples will be stored in this study. All medical records will be kept confidential and will only be reviewed by the participating Investigators. Data will be kept in password-protected computers held at the NEI and Emmes. Only study Investigators and Emmes staff will have access to the study data. The participants' names will not appear on any of the data forms reported to the Coordinating Center. A unique, coded identifier and study registration number will identify the participant if their information is shared with the Coordinating Center for research purposes. Participants' personal information will be kept as private as possible. However, records can be inspected by organizations for quality assurance and data analysis. These include the members of the IRB, the Coordinating Center and the NEI DSMC.

19.0 CONFLICT OF INTEREST

The NIH guidelines were distributed to all the Investigators and none of the Investigators had any conflicts of interest.

20.0 TECHNOLOGY TRANSFER

There are no technology transfer agreements for this study.

21.0 RESEARCH AND TRAVEL COMPENSATION

For this study, there is no compensation for participation. This protocol includes reimbursement for travel, accommodation, and subsistence. At the NEI, participants needing financial assistance will be able to receive supplemental reimbursement based upon need. Requests for supplemental reimbursement will be evaluated on a case-by-case basis for valid financial and/or medical need through a standardized process.

22.0 REFERENCES

1. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology. 1997;104(1):7-21.

2. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992;99(6):933-43.

3. Edwards AO, Ritter R, 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science. 2005;308(5720):421-4.

4. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A. 2005;102(20):7227-32.

5. Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005;308(5720):419-21.

6. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005;308(5720):385-9.

7. Tuo J, Ning B, Bojanowski CM, Lin ZN, Ross RJ, Reed GF, et al. Synergic effect of polymorphisms in ERCC6 5' flanking region and complement factor H on age-related macular degeneration predisposition. Proc Natl Acad Sci U S A. 2006;103(24):9256-61.

8. Cousins SW, Espinosa-Heidmann DG, Csaky KG. Monocyte activation in patients with age-related macular degeneration: a biomarker of risk for choroidal neovascularization? Arch Ophthalmol. 2004;122(7):1013-8.

9. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001;119(10):1417-36.

10. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol. 2002;134(3):411-31.

11. Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in Drusen formation and age related macular degeneration. Exp Eye Res. 2001;73(6):887-96.

12. Rodrigues EB. Inflammation in dry age-related macular degeneration. Ophthalmologica. 2007;221(3):143-52.

13. Buschini E, Piras A, Nuzzi R, Vercelli A. Age related macular degeneration and drusen: neuroinflammation in the retina. Prog Neurobiol. 2011;95(1):14-25.

14. Donoso LA, Kim D, Frost A, Callahan A, Hageman G. The role of inflammation in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2006;51(2):137-52.

15. Gehrs KM, Jackson JR, Brown EN, Allikmets R, Hageman GS. Complement, age-related macular degeneration and a vision of the future. Arch Ophthalmol. 2010;128(3):349-58.

16. Swaroop A, Chew EY, Rickman CB, Abecasis GR. Unraveling a multifactorial late-onset disease: from genetic susceptibility to disease mechanisms for age-related macular degeneration. Annu Rev Genomics Hum Genet. 2009;10:19-43.

17. Crabb JW, Miyagi M, Gu X, Shadrach K, West KA, Sakaguchi H, et al. Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. Proc Natl Acad Sci U S A. 2002;99(23):14682-7.

18. Hollyfield JG, Bonilha VL, Rayborn ME, Yang X, Shadrach KG, Lu L, et al. Oxidative damage-induced inflammation initiates age-related macular degeneration. Nature medicine. 2008;14(2):194-8.

19. Shaw PX, Zhang L, Zhang M, Du H, Zhao L, Lee C, et al. Complement factor H genotypes impact risk of age-related macular degeneration by interaction with oxidized phospholipids. Proc Natl Acad Sci U S A. 2012;109(34):13757-62.

20. Ma W, Coon S, Zhao L, Fariss RN, Wong WT. A2E accumulation influences retinal microglial activation and complement regulation. Neurobiology of aging. 2013;34(3):943-60.

21. Penfold PL, Madigan MC, Gillies MC, Provis JM. Immunological and aetiological aspects of macular degeneration. Progress in retinal and eye research. 2001;20(3):385-414.

22. Gupta N, Brown KE, Milam AH. Activated microglia in human retinitis pigmentosa, late-onset retinal degeneration, and age-related macular degeneration. Exp Eye Res. 2003;76(4):463-71.

23. Ma W, Zhao L, Fontainhas AM, Fariss RN, Wong WT. Microglia in the mouse retina alter the structure and function of retinal pigmented epithelial cells: a potential cellular interaction relevant to AMD. PloS one. 2009;4(11):e7945.

24. Roque RS, Rosales AA, Jingjing L, Agarwal N, Al-Ubaidi MR. Retina-derived microglial cells induce photoreceptor cell death in vitro. Brain research. 1999;836(1-2):110-9.

25. Sennlaub F, Auvynet C, Calippe B, Lavalette S, Poupel L, Hu SJ, et al. CCR2(+) monocytes infiltrate atrophic lesions in age-related macular disease and mediate photoreceptor degeneration in experimental subretinal inflammation in Cx3cr1 deficient mice. EMBO molecular medicine. 2013;5(11):1775-93.

26. Wirostko E, Wirostko WJ, Wirostko BM. Age-related macular degeneration is an inflammatory disease possibly treatable with minocycline. Acta ophthalmologica Scandinavica. 2004;82(2):243-4.

27. Yrjanheikki J, Keinanen R, Pellikka M, Hokfelt T, Koistinaho J. Tetracyclines inhibit microglial activation and are neuroprotective in global brain ischemia. Proc Natl Acad Sci U S A. 1998;95(26):15769-74.

28. Yrjanheikki J, Tikka T, Keinanen R, Goldsteins G, Chan PH, Koistinaho J. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc Natl Acad Sci U S A. 1999;96(23):13496-500.

29. Kraus RL, Pasieczny R, Lariosa-Willingham K, Turner MS, Jiang A, Trauger JW. Antioxidant properties of minocycline: neuroprotection in an oxidative stress assay and direct radical-scavenging activity. Journal of neurochemistry. 2005;94(3):819-27.

30. Pi R, Li W, Lee NT, Chan HH, Pu Y, Chan LN, et al. Minocycline prevents glutamate-induced apoptosis of cerebellar granule neurons by differential regulation of p38 and Akt pathways. Journal of neurochemistry. 2004;91(5):1219-30.

31. Shimazawa M, Yamashima T, Agarwal N, Hara H. Neuroprotective effects of minocycline against in vitro and in vivo retinal ganglion cell damage. Brain research. 2005;1053(1-2):185-94.

32. Krady JK, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW, et al. Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. Diabetes. 2005;54(5):1559-65.

33. Zhao L, Ma W, Fariss RN, Wong WT. Minocycline attenuates photoreceptor degeneration in a mouse model of subretinal hemorrhage microglial: inhibition as a potential therapeutic strategy. The American journal of pathology. 2011;179(3):1265-77.

34. Yoshida N, Ikeda Y, Notomi S, Ishikawa K, Murakami Y, Hisatomi T, et al. Laboratory evidence of sustained chronic inflammatory reaction in retinitis pigmentosa. Ophthalmology. 2013;120(1):e5-12.

35. Hughes EH, Schlichtenbrede FC, Murphy CC, Sarra GM, Luthert PJ, Ali RR, et al. Generation of activated sialoadhesin-positive microglia during retinal degeneration. Investigative ophthalmology & visual science. 2003;44(5):2229-34.

36. Roque RS, Imperial CJ, Caldwell RB. Microglial cells invade the outer retina as photoreceptors degenerate in Royal College of Surgeons rats. Invest Ophthalmol Vis Sci. 1996;37(1):196-203.

37. Zeng HY, Tso MO, Lai S, Lai H. Activation of nuclear factor-kappaB during retinal degeneration in rd mice. Molecular vision. 2008;14:1075-80.

38. Zeng HY, Zhu XA, Zhang C, Yang LP, Wu LM, Tso MO. Identification of sequential events and factors associated with microglial activation, migration, and cytotoxicity in retinal degeneration in rd mice. Invest Ophthalmol Vis Sci. 2005;46(8):2992-9.

39. Hughes EH, Schlichtenbrede FC, Murphy CC, Broderick C, van Rooijen N, Ali RR, et al. Minocycline delays photoreceptor death in the rds mouse through a microglia-independent mechanism. Exp Eye Res. 2004;78(6):1077-84.

40. Yang LP, Li Y, Zhu XA, Tso MO. Minocycline delayed photoreceptor death in rds mice through iNOS-dependent mechanism. Molecular vision. 2007;13:1073-82.

41. Salamon SM. Tetracyclines in ophthalmology. Surv Ophthalmol. 1985;29(4):265-75.

42. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. Clin Ther. 2005;27(9):1329-42.

43. Lampl Y, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A, et al. Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. Neurology. 2007;69(14):1404-10.

44. Cukras CA, Petrou P, Chew EY, Meyerle CB, Wong WT. Oral minocycline for the treatment of diabetic macular edema (DME): results of a phase I/II clinical study. Investigative ophthalmology & visual science. 2012;53(7):3865-74.

45. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol. 2007;143(3):463-72.

46. Sunness JS, Margalit E, Srikumaran D, Applegate CA, Tian Y, Perry D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. Ophthalmology. 2007;114(2):271-7.

47. Choudhry N, Giani A, Miller JW. Fundus autofluorescence in geographic atrophy: a review. Seminars in ophthalmology. 2010;25(5-6):206-13.

48. The Age Related Eye Disease Study 2 Research Group (AREDS2), Chew E, Clemons T, SanGiovanni J, Danis R, Ferris Fr, et al. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. Jama. 2013;309(19):2005-15.

49. Wagner A, Soumerai S, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27:299-309.

50. Fitzmaurice G, Laird N, Ware J. Modeling the Mean: Parameteric Curves. Applied Longitudinal Analysis. 2011;2nd ed,pp. 149-151. Hoboken, NJ: Wiley.

APPENDIX 1: DETERMINING CHILDBEARING POTENTIAL

A female participant who is considered non-childbearing due to a medical condition (i.e., participant has previously undergone a hysterectomy) does not need a pregnancy test, Follicle-stimulating Hormone (FSH) test or contraception.

If a female participant is considered non-childbearing due to menopause, it must be in accordance with the NIH OB-GYN guidance on the definition of menopause. This guidance defines menopause as:

- Women over age 55 who have not had a period for one year will be considered menopausal and do not need a pregnancy test, FSH test or contraception.

- Women age 55, who have not had a period for one year, should have an FSH test. If their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and do not need pregnancy testing or contraception. If their FSH level is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.

APPENDIX 2: STUDY FLOWSHEET

	Run-in Phase			**Treatment Phase**									
Visit Schedule[1] (Month)	**0**	**3**	**6**	**9**	**12**	**15**	**21**	**27**	**33**	**39**	**45**	**51[2]**	**57[2]**
Visit Number	000	003	006	009	012	015	021	027	033	039	045	051	057
Target Visit Day	0	90	180	272	365	455	637	820	1002	1190	1371	1555	1735
Treatment[5]													
Dispense Investigational Product (taken twice daily)[3]				X	X	X	X	X	X	X	X[4]	X[4]	X[4]
Drug Accountability Review					X	X	X	X	X	X	X	X	X
General Assessments[5]													
Medical/Ophthalmic History	X												
Concomitant Medications				X	X	X	X	X	X	X	X	X	X
Vital Signs				X	X	X	X	X	X	X	X	X	X
Thyroid Palpation[6]	X			X		X	X	X	X	X	X	X	X
Physical Examination	X[8]												
Adverse Event Assessment					X	X	X	X	X	X	X	X	X
Ophthalmic Assessments[5]													
BCVA (EVA)	X[9]	X	X	X	X	X	X	X	X	X	X	X	X
Manifest Refraction	X[9]	X	X	X	X	X	X	X	X	X	X	X	X
Low-luminance visual acuity[10]	X[9]	X		X		X	X	X	X	X	X	X	X
Slit Lamp Examination	X[9]	X	X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure (IOP)	X[9]	X	X	X	X	X	X	X	X	X	X	X	X
Stereoscopic Color Fundus	X[7]	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Autofluorescence (FAF) and Infrared Reflectance Imaging	X[7]	X	X	X	X	X	X	X	X	X	X	X	X

	Run-in Phase			**Treatment Phase**									
Visit Schedule[1] (Month)	**0**	**3**	**6**	**9**	**12**	**15**	**21**	**27**	**33**	**39**	**45**	**51[2]**	**57[2]**
Visit Number	000	003	006	009	012	015	021	027	033	039	045	051	057
Target Visit Day	0	90	180	272	365	455	637	820	1002	1190	1371	1555	1735
Microperimetry [12]	X[7]	X		X		X	X	X	X	X	X	X	X
Optical Coherence Tomography (OCT)	X[7]	X	X	X	X	X	X	X	X	X	X	X	X
Fluorescein Angiography				X[13]									
Laboratory Assessments[5,8]													
Acute Care Panel	X[8]			X		X	X	X	X	X	X	X	X
Hepatic Panel	X[8]			X		X	X	X	X	X	X	X	X
Complete Blood Count (CBC)	X[8]			X		X	X	X	X	X	X	X	X
Thyroid Function Test (TFT)	X[8]			X		X	X	X	X	X	X	X	X
Pregnancy Test[11]	X[8]			X		X	X	X	X	X	X	X	X

1 All visits must be conducted within a window of ±30 days from the target visit day.

2 These visits are for participants who enrolled at the beginning of the study and continue until the common termination date. The common termination date is reached when the last recruited participant has received 36 months of IP. Participants may complete participation in the study as early as Month 45, at the discretion of the investigator. Participants who complete the Month 57 visit may terminate the study at the same visit or return for a final (supplemental) visit to terminate from the study.

3 Participants will take an IP capsule two times a day, once in the morning and once in the evening, approximately 12 hours apart. At the time the IP is dispensed, an information sheet outlining instructions on taking IP and concomitant medications will be provided to the participant.

4 IP will only be dispensed at these visits for participants who enrolled at the beginning of the study and continue IP until the common termination date. If a participant is terminating at this visit, IP will not be dispensed.

5 In the event that the testing was not completed within a day, subsequent clinic visits may be scheduled within 10 days of the first visit to complete the scheduled evaluation.

6 The internal medicine consult service will perform the thyroid palpation for Visit 000 and will communicate the results to the Investigators. The study Investigators will perform the same thyroid palpation at each study visit, beginning at Month 9. Any clinically significant abnormalities on thyroid palpation and/or TFT will prompt a referral to an endocrinologist.

[7] Indicated assessment may be performed under NIH Protocol 08-EI-0102, NIH Protocol 08-EI-0169, NIH 08-EI-0043, NIH 12-EI-0042, or NIH 11-EI-0147 if performed within 30 days prior to the initial study visit.

[8] Indicated assessment may be performed under NIH Protocol 08-EI-0102, NIH Protocol 08-EI-0169, NIH 08-EI-0043, NIH 12-EI-0042, or NIH 11-EI-0147 if performed within 60 days prior to the initial study visit.

[9] If the indicated assessment was previously performed under NIH Protocol 08-EI-0102, NIH Protocol 08-EI-0169, NIH 08-EI-0043, NIH 12-EI-0042, or NIH 11-EI-0147 for screening, the assessment will be repeated at time of enrollment.

[10] The procedure will be performed on study eye and the qualifying fellow eye. Evaluations on non-qualifying fellow eyes may be performed for routine clinical evaluation for the continuing care of the participant as determined by the treating investigator.

[11] For women of childbearing potential only, participants must have a negative pregnancy test within 24 hours prior to dispensation of IP. See Appendix 1 for guidance on determining whether a female is considered to be of childbearing potential.

[12] Mesopic microperimetry will be performed on study eyes and scotopic microperimetry will be performed on qualifying fellow eyes. If a participant is unable to complete microperimetry testing, the testing may be waived for subsequent study visits and the investigator will specify the reason the test could not be completed.

[13] FA will only be performed if the absence of CNV cannot be definitively ascertained after review of retinal images.

APPENDIX 3: GEOGRAPHIC ATROPHY GRADING PROCEDURES FROM DIGITIZED PHOTOGRAPHS

GA will be assessed from the color fundus photographs. GA is observed as one of more sharply defined patches of partial or complete depigmentation of the retinal pigment epithelium (RPE), typically with exposure of underlying large choroidal blood vessels. In general at least two of the aforementioned characteristics (sharp edges, more or less circular shape and visibility of underlying choroidal vessels) are required for a lesion to be classified as GA. Thus, even if much of the RPE appears to be preserved and large choroidal vessels cannot be seen, a roundish patch of RPE depigmentation with sharp edges may still be classified as GA. The criterion of "edge sharpness" may be fulfilled in either of two ways: (1) when the depigmentation within the patch is subtle, a "sharp" edge must be abrupt and smooth, like one made with a cookie cutter, or (2) when contrast between depigmentation within a patch and the normal depigmentation around it is substantial, the edge of the patch may still be considered "sharp" even if the transition occurs gradually or irregularly over a zone of 125 to 250 μm in width. Increased visibility of large choroidal vessels is the single most important criterion and, when present, it is not necessary for all the edges of the patch to be sharp (25% of its circumference may be sufficient).

Longitudinal analysis of each patient is performed as a quality control measure in order to ensure consistency in borderline decisions regarding the extent of GA.

Once GA has been identified on the FAF by the grader, the grader will manually outline the GA lesion(s) using the Doheny Image Reading & Research Lab GRADOR software. All areas of GA will be outlined. Then, using the results generation function of the GRADOR, the pixel counts within the outlined area(s) will be converted to areas, in units of both MPS DA and mm^2.

APPENDIX 4: PARTICIPANT REMINDERS

Participant Reminders

1. *On the day of your fourth visit, you will receive your first supply of your study medication. On that day, you will take one pill in the evening. On the next day and all other days of the study, you will take two pills every day, one in the morning and one in the evening. Take them at approximately the same time every day, approximately 12 hours apart, to help you to remember to take them.*
2. *Take your pills with a full glass (eight ounces) of water or more.*
3. *Do not take iron, multivitamins, calcium supplements, antacids or laxatives within two hours before or after taking your study medication. These products may make your study medication less effective.*
4. *If you vomit after taking your pill, do not repeat a dose. Contact the Principle Investigator or NEI Study Coordinator about vomiting or ANYTHING else that you feel is a side effect.*
5. *If you forget to take a pill and it is less than six hours after the missed dose, you should take the pill when you remember and take the next dose at your regularly scheduled time. If you forget to take a pill and it is more than six hours after the missed dose, you should skip that dose and take the next dose at your regularly scheduled time.*
6. *Your pills should be stored at room temperature (59 - 86° F). They should be protected from light, moisture, and excessive heat.*
7. *Please inform any doctor who is prescribing new medication that you may be taking minocycline. If a new medication is prescribed to you, please inform a study team member at your next visit. If you are prescribed any new antibiotics, please contact a study team member immediately.*

   Please be aware that minocycline can reduce or prevent some medications from working. Medications, such as penicillin, may not work when taking minocycline.
8. *Remember to bring your pill bottles and any leftover pills with you to all appointments.*
9. *We will supply you with study medication at every visit. If for any reason you miss a study visit, contact a member of the study team so that your appointment can be rescheduled and arrangements made to supply you with your study medication.*
10. *If you develop diarrhea while you are enrolled in this study, seek medical attention promptly.*
11. *While taking this study medicine, you should:*
    - *Wear protective clothing, including a hat and sunglasses whenever you are outside.*
    - *Apply a sun block product that has a skin protection factor (SPF) of at least 15 to your skin and a sun block lipstick to your lips. Those who have a fair complexion should use sunblock with a higher SPF number.*
    - *Use extra caution near water, snow and sand because they reflect and intensify the damaging rays of the sun.*

- *Not use a sunlamp or tanning bed or booth.*

You may still be more sensitive to sunlight or sunlamps for two weeks to several months or more after stopping this medicine. If you have a severe reaction, see your doctor immediately.

12. *Remember, if you are a woman who is able to get pregnant or if you are a man able to father children, you (or your partner) must have had a hysterectomy or a vasectomy, be completely abstinent from intercourse or be willing to use two effective methods of birth control while in this study and for one week after you stop taking the study pills.*

    Please be aware that minocycline can make hormonal contraceptives less effective and increase the risk of pregnancy.

    Acceptable methods of birth control for this study include the combined use of TWO of the following methods:

    1. *hormonal contraception (birth control pills, injected hormones, skin patch or vaginal ring),*
    2. *intrauterine device*
    3. *diaphragm with spermicide or a condom with spermicide, or*
    4. *tubal ligation.*

    A gynecologist will advise you on the acceptable methods of birth control.

Contact your study team with any questions:

Study Coordinator: *NAME* *CONTACT NUMBER*

Principal Investigator: *NAME* *CONTACT NUMBER*

Please note: If any questions or issues arise after normal business hours or on the weekend, you may call EMERGENCY AFTER HOURS CONTACT. Be sure to identify the study you are on.

YOUR STUDY IS: 15-EI-0202

"Pilot Study for the Evaluation of Oral Minocycline in the Treatment of Geographic Atrophy Associated with Age-Related Macular Degeneration"