

Evaluation of Alpha Lipoic Acid as a Potential Treatment for Geographic Atrophy in subjects with Age-related Macular Degeneration

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List of Abbreviations

ALA: Alpha Lipoic Acid

AMD: Age-related macular degeneration

BCVA: Best-corrected visual acuity as measured by an electronic visual acuity (EVA) or ETDRS chart

CPOB: Center for Preventive Ophthalmology and Biostatistics

DA: Optic disc area

EAE: Experimental autoimmune encephalomyelitis

FAF: Fundus autofluorescence

GA: Geographic atrophy is defined as one or more well-defined, more or less circular patches of loss of the RPE, typically with exposure of underlying choroidal blood vessels

OCT: Spectral Domain Optical Coherence Tomography

RPE: Retinal pigment epithelium

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Study Summary

Title	Evaluation of Alpha Lipoic Acid as a Potential Treatment for Geographic Atrophy in subjects with Age-related Macular Degeneration
Short Title	Lipoic Acid in GA
Protocol Number	822310
Clinical Trial Phase	II
Methodology	Dose tolerability test (Phase 1) Randomized, double-blind, placebo-controlled (Phase 2 Pilot Study).
Study Duration	<u>Phase 1</u> : 15 days <u>Phase 2</u> : 31 months: 12 month enrollment period followed by an approximately 1 month run-in period and then an 18 month study participation after randomization. (Final subject could have final study visit 31 months after first study subject was screened)
Study Center(s)	Phase 1: Single site (1 site); Phase 2: Multi-site (5 total)
Objectives	The objective of Phase 1 of this protocol is to ensure that oral Alpha Lipoic Acid doses of up to 1200 mg daily are well-tolerated in the elderly population. The objective of Phase 2 of this protocol is to determine the effects of ALA on the progression of GA in patients with AMD through a Phase II pilot clinical trial.
Number of Subjects	65 subjects (Phase 1: 15; Phase 2: 50)
Main Inclusion Criteria	<ul style="list-style-type: none"> • Age 55-90 • Diagnosis of geographic atrophy from age-related macular degeneration in the study eye. The largest GA lesion must be a minimum of 0.5 DA (1.25 mm²) and no more than 6 DA in size. GA is defined as one or more well-defined, usually more or less circular patches of loss of the RPE, typically with exposure of underlying choroidal blood vessels. If the GA is multifocal and the largest lesion is < 0.5 DA, then there should be at least 3 lesions ≥ 250 microns in greatest linear diameter. • BCVA between 20/20 and 20/400 in the study eye. • Presence of hyperfluorescence at the edge of GA on autofluorescence imaging.
Investigational Product	Alpha Lipoic Acid (ALA), also known as Thioctic Acid.
Duration of administration	Phase 1: 15 days Phase 2: 18 months from the time of randomization
Reference therapy	The reference is a placebo.

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**Statistical
Methodology**

For Phase 1 of this protocol, the percent of adverse events and serious adverse events that developed in the study group will be determined. For Phase 2 of this protocol, the mean change in the total area of GA within study eyes over 18 months will be compared between subjects receiving the active ALA dose and placebo supplementation; a square root transformation will be applied to the area measurements to mitigate the dependence of growth rate on initial size.

Safety Evaluations

For Phase 1 of this protocol, the primary safety outcome is the percent of subjects that develop a serious adverse event while taking ALA. For Phase 2 of this protocol, the primary safety outcome will be a visual acuity decrease of ≥ 3 lines (15 letters) between baseline and 18 months after randomization.

**Data and Safety
Monitoring Plan**

Monitoring is risk based.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance with University of Pennsylvania Research Policies, Procedures, Federal and State regulations, and in accordance with international standards of Good Clinical Practice (GCP).

Introduction

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) for which there is currently no available treatment. Damage to the retina secondary to oxidative stress is thought to be a significant factor in the pathogenesis of GA.¹⁻³ Recently, the Dunaief Lab at the University of Pennsylvania has found that alpha lipoic acid (ALA), a potent antioxidant and iron chelator, is extremely retina-protective in a light damage mouse model.⁴ ALA, a naturally occurring substance made by the body, is an excellent candidate drug because it has proven to be safe and effective during decades of use for the treatment of diabetic peripheral neuropathy.⁵⁻⁸ The objective of this study is to determine the effects of ALA on the progression of GA in patients with AMD through a Phase II clinical trial. The central hypothesis is that oral ALA supplementation reduces the rate of enlargement of GA in AMD patients. The rationale is that the antioxidant and iron chelating effects of ALA will slow down one of the major pathways responsible for GA progression.

1.1 Background and Relevant Literature

Age-related macular degeneration (AMD) is a complex, degenerative, and progressive eye disease that can result in severe loss of central vision. It is the leading cause of blindness among those 60 years or older in the Western hemisphere.⁹⁻¹⁰ Geographic atrophy (GA), an advanced form of AMD, is responsible for approximately 20% of the legal blindness cases in North America.¹ Based on United States (US) Census Bureau data from the year 2000 and AREDS (Age Related Eye Disease Study) data, there are at least an estimated 824,000 individuals in the US of at least 55 years of age with geographic atrophy.¹¹ Presently, this number is likely higher given the population growth in this age category. Similarly, there are at least 8 million individuals in the US with monocular or binocular intermediate AMD or monocular advanced AMD, and thus at risk for progression to advanced AMD in one of their eyes. The major mechanisms involved in AMD progression include oxidative stress, inflammation with abnormalities in the complement system, accumulation of lipid peroxidation end products, and the production of other toxic metabolic byproducts from the visual cycle.^{1,12-15} Iron potentially contributes to the oxidative damage seen in AMD.¹⁶⁻¹⁸

AMD is characterized by a progressive degeneration of the macula, leading to a severe decrease in central vision. An early sign of AMD is the appearance of drusen, which are yellow, extracellular deposits that accumulate below the retinal pigment epithelium (RPE) and are known to be risk factors for developing choroidal neovascularization (CNV). Depending on the number and size of drusen at the macula, a subject may be categorized as intermediate AMD.¹⁹ Some of these subjects may progress to advanced AMD. There are two types of advanced AMD: GA and exudative (neovascular) AMD. GA can be defined as one or more well-defined, more or less circular patches of loss of the RPE, typically with exposure of underlying choroidal blood vessels. GA can be multifocal or unifocal. Areas of GA are atrophic, nonfunctioning retina, and each area of GA leads to a scotoma in the subject's visual field. Exudative AMD is defined as the presence of abnormal vessels, referred to as choroidal neovascularization, under the retina or retinal pigment epithelium. These vessels can leak fluid and bleed, leading to acute and severe vision loss. The current standard-of-care treatment of exudative AMD is intravitreal injection therapy with anti-VEGF (vascular endothelial growth factor) agents.²⁰ For eyes with geographic atrophy, 2 – 18% may develop CNV over the course of two years, and CNV in the fellow eye is a risk factor for this development.²¹ There currently is no treatment to prevent or slow the progression of GA.

Several Phase I and Phase II clinical trials have evaluated agents targeting the mechanisms of GA,²²⁻²⁶ but there has been very limited success. Stem cell therapy holds promise but is an area where more work is needed to clearly show safety and efficacy in humans.²⁷⁻²⁸ Thus far, the only therapeutic agent that has progressed to a Phase III trial is lampalizumab, an inhibitor of complement factor D, and this trial

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is estimated to be complete in 2018.²⁹⁻³⁰ If lampalizumab is shown to be an effective treatment for GA, then there is still a significant need for other treatments for GA that may add to its effect or reduce its treatment burden, especially since lampalizumab may require intravitreal injection every 4 or 6 weeks. Thus, there is a critical need to find a treatment for GA that can slow its progression or prevent its onset. In the absence of such a treatment, a tremendous number of people will continue to become legally blind.

1.2 Name and Description of the Investigational Product

Alpha lipoic acid (ALA) is also known as thioctic acid. Placebo product is also used in this study. ALA is a potent antioxidant that was approved many years ago in Germany for the treatment of diabetic peripheral neuropathy.⁵⁻⁸ ALA is created endogenously by plants and animals. It is available in the diet through potatoes, spinach, broccoli, tomatoes, peas, brussel sprouts, and rice bran.³¹ It can already be purchased as an over-the-counter supplement and is manufactured by several companies. ALA is an important cofactor for mitochondrial enzyme complexes and is involved in the metabolic process that converts carbohydrates into energy.³² The functions of ALA also include the restoration of diminished levels of other antioxidants, acting as a potent chelator of metal ions such as iron, stimulating glucose uptake, and increasing insulin sensitivity.³²

1.2.1 Nonclinical Data

Recently, the Dunaief Lab of the University of Pennsylvania found that ALA, a potent antioxidant and iron chelator, is extremely retina-protective in a light damage mouse model.⁴ While there is no animal model that exactly replicates GA from AMD, the mouse model of light-induced retinal degeneration is a good model for studying the development of retinal atrophy. The Dunaief Lab found that intraperitoneal ALA given daily at 100 mg/kg had a significant protective effect in a mouse model of light-induced retinal degeneration. ALA, a naturally occurring substance made by the body, is an excellent candidate drug because it has proven to be safe and effective during decades of use for the treatment of diabetic peripheral neuropathy.⁵⁻⁸ ALA is widely available over the counter. Additionally, animal model data has shown that ALA potentially restores tear production and, thus, may be of benefit for the treatment of dry eye disease and its symptoms.³³

1.2.2 Clinical Data to Date

ALA has been approved for the treatment of diabetic peripheral neuropathy for many years in Germany.⁵⁻⁸ It also has been studied in clinical trials for a variety of diseases including cardiovascular disease, diabetes, schizophrenia, and others.³⁴ It is commonly used at doses of 200-600 mg and is already available over-the-counter.

The safety of ALA has been extensively evaluated. ALA is metabolized by the liver and is known to be safe in both hepatic and renal disease. The primary side effects from oral ALA are gastrointestinal and occur at doses of 1200 mg or higher. These gastrointestinal side effects predominantly involve an upset stomach, gastric reflux, nausea, and can be minimized if ALA is taken in divided doses or with a meal, although concurrent food ingestion may partially reduce the bioavailability.³⁵⁻³⁷ There can also be a malodorous urine and headache. Rare complications that may be related to ALA include one subject that developed an allergic rash, fever, and mild thrombocytopenia that resolved after stopping ALA and reports of a rare occurrence of insulin autoimmune syndrome.³⁸⁻³⁹ Insulin autoimmune syndrome is treatable and resolves within a few months after cessation of ALA. Most of these published studies on the safety and tolerability of ALA at doses of 1200 mg or higher involve adults that are not elderly.

1.2.3 Human Pharmacokinetics

ALA is both water and fat-soluble. Importantly, it is known to cross the blood-brain barrier and is therefore capable of reaching the target ocular tissues.⁴⁰⁻⁴¹ There are two enantiomers (R and S) of ALA, and the R form is the naturally occurring form.⁴² Many clinical studies have used the racemic form of ALA and biological activity has been shown with oral ingestion of the racemic form.^{5,36,43} When the oral form is ingested, gastrointestinal absorption is roughly 30%.⁴⁴ Yadav et al. and other groups have reported pharmacokinetic data on oral, racemic ALA from different companies, including ALA from Pure Encapsulations (Sudbury, MA), a subsidiary of Atrium Innovations Inc. (Westmount, Canada). They

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showed that when ALA is taken with food, maximum blood levels are achieved 30-60 minutes after ingestion.^{35,42} Peak levels in the cortex, retina, and optic nerve are achieved around the same time.⁴⁵⁻⁴⁶ Doses of 600 mg twice daily led to median serum levels of 0.2 µg/mL (range 0 - 3.7 µg/mL), while median serum levels of ALA after placebo ingestion were negligible (all values < 1 µg/mL).³⁶ Doses of 1200 mg daily or twice daily led to median serum levels of 4.8 µg/mL (range 0 – 19 µg/mL). When taking 1200 mg daily, blood levels of ALA are undetectable approximately 5 hours after ingestion.³⁵

1.3 Dose Rationale

The Dunaief Lab found that intraperitoneal ALA given daily at 100 mg/kg had a significant protective effect in a mouse model of light-induced retinal degeneration.⁴ Others have shown oral ALA at similar doses to be protective of retinal ganglion cells in a mouse model of glaucoma.⁴⁵ Yadav et al. found that subcutaneous injections of ALA at 50 mg/kg/day was an effective dose at suppressing experimental autoimmune encephalomyelitis (EAE) in mice. They then found that 1200 mg of oral ALA taken daily with a meal led to a comparable peak serum level as the peak serum level seen in mice when EAE is suppressed by ALA, and they concluded that 1200 mg daily with a meal would be an effective and tolerable dose to test for multiple sclerosis.³⁵ With concurrent food ingestion, the potential gastrointestinal side effects are minimized. Thus, 1200 mg daily with a meal has the potential to be efficacious, safe, and well tolerated. This study will be conducted in two parts. The first part is the dose tolerability test (Phase 1). In Phase 1, doses of 600 mg daily, 800 mg daily, and 1200 mg daily of oral ALA will be tested in subjects in the elderly population, as most safety/tolerability data for higher doses of ALA is not specific to the elderly population. Once the first Phase is complete a randomized, double-blind placebo controlled trial (Phase 2) will be conducted. In Phase 2, doses of 1200mg will be administered to subjects for 18 months, assuming that 1200 mg is well-tolerated by subjects in Phase 1. If 1200 mg is not well-tolerated based on Phase 1 data, then the highest tolerable dose will be used.

2 Study Objectives

The objective of Phase 1 of this protocol is to determine if doses of 600 mg, 800 mg, and 1200 mg of ALA are well-tolerated in the elderly population as each dose is taken for 5 days.

The objective of Phase 2 of this protocol is to determine the effects of ALA on the progression of GA in subjects with AMD. The central hypothesis, based on the existing literature, is that oral ALA reduces the rate of enlargement of GA in AMD subjects. The rationale is that the antioxidant and iron chelating effects of ALA will slow down one of the major pathways responsible for GA progression.

2.1 Primary Objective

The primary objective is to investigate ALA's effect on the rate of change over time (18 months) in area of GA in the study eye, as determined by masked digital grading of fundus photography. The primary endpoint will be determined using fundus autofluorescence (FAF). The study will utilize the Scheie Eye Institute Reading Center to grade the photographs.

2.2 Secondary Objectives

The secondary objectives investigate the effect of ALA on the following:

- Change in best-corrected visual acuity (BCVA)
- Three line or more worsening from baseline BCVA
- Absolute and relative change in area of GA as measured on FAF
- Rate of change over time (18 months from the time of randomization) in area of GA in the study eye as measured on color fundus photos.
- Absolute and relative change in area of GA as measured on color fundus photos
- Ocular safety outcomes of ALA as indicated by changes in visual acuity, development of uveitis, or any other ocular changes not consistent with the natural progression of GA

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The following exploratory endpoints will be of interest to the study: 1) Change in drusen volume based on OCT and change in the number of drusen seen on color fundus photos; 2) Change in score on the Ocular Surface Disease Index (OSDI)⁴⁷; 3) Change in best distance corrected near visual acuity.

3 Investigational Plan

3.1 General Design

Phase 1: Dose tolerability test

This is a single site dose tolerability test. We plan to enroll 15 subjects (ages 65-90) in a single site drug tolerability test. Each enrolled subject will take 600 mg of oral ALA once daily with a meal for 5 days. If well-tolerated, each subject will then take 800 mg of oral ALA once daily with a meal for 5 additional days. If 800 mg of oral ALA is well-tolerated, then subjects will then take 1200 mg of oral ALA once daily with a meal for 5 days.

Phase 2: Randomized, double-blind placebo controlled pilot trial

Upon the completion of the dose tolerability test, we plan to enroll 50 subjects into a randomized, double-blind, placebo-controlled trial. Subjects will be randomized (1:1) into one of two study arms: placebo capsules and ALA 1200 mg orally once daily, assuming that 1200 mg is well tolerated by subjects in Phase 1. If 1200 mg is not well-tolerated based on Phase 1 data, then the highest tolerable dose will be used. Four clinical sites are planned and the enrollment period is estimated to be 12 months. The primary endpoint is the mean rate of change of the area of GA in the study eye from baseline to 18 months (from the time of randomization) as evaluated by fundus autofluorescence. Subjects will have a refracted electronic visual acuity and dilated exam at baseline, 6 months, 12 months, and 18 months.⁴⁸ The study will be conducted on an outpatient basis and study visits will last approximately 2-3 hours. Two weeks after the 18 months study visit, the subject will be contacted to share with the investigators adverse events that developed after completing the 18 month visit. The Investigator shall ensure each subject has a follow-up eye exam scheduled within 6 months.

3.1.1 Allocation to Interventional Group

Phase 1- Tolerability

For the tolerability test (Phase 1), 15 subjects will each take ALA at doses of 600 mg, 800 mg, and 1200 mg daily. There is no randomization for the tolerability test. The 15 subjects will receive the ALA after consenting to the tolerability study at the Scheie Eye Institute of the University of Pennsylvania.

Phase 2

Screening/Run-In Phase

After the clinician determines the patient meets preliminary eligibility for the trial and the patient signs the consent form, the screening data will be entered into the data management system. Coordinating Center staff will verify the patient is eligible for the study; correction or confirmation will be performed as needed. The Clinical and Scientific Expert and the Scheie Eye Institute Reading Center will also review the patient's information and retinal images to confirm eligibility prior to randomization and complete a form confirming eligibility that is entered into the data management system.

At the screening visit, all subjects will be provided with a postage-paid mailing envelope. Those subjects that do not meet inclusion and exclusion criteria will be contacted and informed that they did not meet all of the screening criteria. Those subjects that are meeting inclusion and exclusion criteria will be instructed to start the 10 day run-in phase, once they receive the medication bottle in the mail. The UPenn Investigational Drug Service will mail a medication bottle with 10 placebo capsules to the subject. The shipment will include instructions for taking the capsules and a form for providing the first and last dates of taking the capsules. After completing the 10 days of the run-in phase, the subject will use the postage-paid mailing envelope to mail back the medication bottle, any remaining contents, and the form to the clinical site. The subject is not informed of whether the study capsules for the run-in phase are placebo or ALA.

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Subjects who demonstrate compliance by taking $\geq 80\%$ of the provided capsules and mailing the medication bottle within 40 days of the screening visit will be eligible to continue in the study. If an investigator did not receive a mailed medication bottle but believes the subject followed instructions and the medication bottle was lost in the mail, then that subject may get screened again for the study. In this instance, the subject will have to repeat the screening visit and the run-in phase.

Intervention Phase

The Coordinating Center is responsible for random assignment of patients to one of the two treatment groups. Random treatment allocation schedules will be generated using a randomized block design and stratified by clinical center. All baseline procedures must be performed within 40 days of the day of randomization.

For subjects who have successfully completed the run-in phase, the clinical site will inform the Coordinating Center that that all inclusion and exclusion criteria have been met. Coordinating Center staff will issue the next randomized treatment assignment from the clinical site's schedule for the patient. A Coordinating Center staff member notifies the clinical site Investigator that the randomization has been completed and the Investigator will fax/send a prescription for study medication (ALA or placebo), signed by the Principal or Sub-Investigator, to the University of Pennsylvania's Investigational Drug Service (IDS). A Coordinating Center staff member will notify IDS of the treatment assignment.

Once IDS receives both the prescription from the Investigator and the treatment assignment from the Coordinating Center, IDS will send a supply of study drug to the subject's home. Subsequent study medication also will be mailed by IDS directly to the subject's home.

For both study Phases, prior to starting the medication, the subject will be instructed on how to take the medication, and what signs and symptoms to monitor and report. For Phase 2 of the protocol, each subject will be contacted approximately two weeks after randomization to verify that the study drug has been received and that each subject is taking the study medication per instructions.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

For Phase 1 of this protocol, the primary endpoint is the percent of adverse events that develop in the study group.

For Phase 2 of this protocol, the primary endpoint is the rate of change over time (18 months from the time of randomization) in area of GA in the study eye. This is determined by masked grading of FAF, in participants randomized to placebo or 1200 mg once daily of ALA.

3.2.2 Secondary Study Endpoints

The secondary endpoints will investigate the effect of ALA on the following:

- Absolute and relative change in area of GA as measured on FAF
- Rate of change over time (18 months from the time of randomization) in area of GA in the study eye as measured on color fundus photos
- Absolute and relative change in area of GA as measured on color fundus photos
- Ocular safety outcomes of ALA as indicated by changes in visual acuity, development of uveitis, or any other ocular changes not consistent with the natural progression of GA

The following exploratory endpoints will be of interest to the study: 1) Change in drusen volume based on OCT and change in the amount of drusen on color fundus photos; 2) Change in score on the Ocular Surface Disease Index (OSDI).⁴⁷; 3) Change in best distance corrected near visual acuity.

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3.2.3 Primary Safety Endpoints

The primary safety endpoint is a change in best-corrected visual acuity (BCVA) that involves a loss of three lines or more from baseline.

4 Study Population and Duration of Participation

4.1 Dose Tolerability Test (Phase 1)

4.1.1 Inclusion Criteria

- Ages 65-90
- Female participants must be menopausal. Male participants are required to use contraception.
- Able to give informed consent
- For the study duration (15 days), the subject must remain in the country, remain within 4 hours of travel time (by car or airplane), have access to medical care if needed, and provide contact information so the subject can be reached as needed.

4.1.2 Exclusion Criteria

- Blood Pressure greater than 190/100 at the baseline visit
- Pulse greater than 100 at the baseline visit
- Acute and ongoing systemic infection
- History of dementia
- Participant has a condition that, in the opinion of the investigator, gives them an unstable medical status.
- Participant has geographic atrophy and the investigator believes the participant is a candidate for enrollment into Phase 2 of this trial.

4.1.3 Subject Recruitment

Subjects will be recruited from the investigator's site (Scheie Eye Institute of the University of Pennsylvania)

4.1.4 Duration of Study Participation

Subjects will participate in the ALA tolerability test for 15 days.

4.1.5 Total Number of Subjects and Sites

15 subjects will be recruited from a single site (Scheie Eye Institute of the University of Pennsylvania) for the ALA tolerability test.

4.1.6 Vulnerable Populations

No vulnerable populations will be involved with this study.

4.2 Randomized, double-blind placebo controlled trial (Phase 2)

4.2.1 Inclusion Criteria

- Age 55-90
- Diagnosis of geographic atrophy from age-related macular degeneration in the study eye. The largest GA lesion must be a minimum of 0.5 DA (1.25 mm²) and no more than 6 DA in size (15.0 mm²). GA is defined as one or more well-defined, usually more or less circular patches of loss of the RPE, typically with exposure of underlying choroidal blood vessels. If the GA is multifocal and the largest lesion is < 0.5 DA, then there should be at least 3 lesions ≥ 250 microns in greatest linear diameter.
- BCVA between 20/20 and 20/400 in the study eye.
- Female participants must be menopausal. Male participants are required to use contraception and cannot donate sperm during study participation.
- Presence of hyperfluorescence at the edge of GA on autofluorescence imaging.

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- Ability to give informed consent.
- If a subject has two eligible eyes, then both eyes can be enrolled into the study.
- Subject must have mailed back the medication bottle after the 10 day run-in phase, demonstrating that they have taken $\geq 80\%$ of the capsules.

4.2.2 Exclusion Criteria

- Evidence of ocular disease other than AMD in the study eye that may confound the study outcomes (e.g., History of myopic degeneration, choroidal neovascularization, central serous chorioretinopathy, severe diabetic retinopathy, uveitis, vitelliform dystrophy, or macular edema).
- Presence of geographic atrophy that is already touching clearly defined beta peripapillary atrophy or is already touching the optic disc. Beta peripapillary atrophy is defined as peripapillary atrophy in which either the sclera or choroidal vessels are clearly visible.
- Any history of intravitreal injection in the study eye for AMD or choroidal neovascularization. However, if a subject develops choroidal neovascularization in the study eye *during* the study, then the subject will receive the standard of care intravitreal injection treatments per the investigator. The subject will continue to stay in the study. Treatment of CNV or other diseases in the non-study eye is at the investigator's discretion.
- History of intravitreal injection of any agent (e.g., triamcinolone) other than anti-VEGF in the study eye within the last four months prior to study enrollment.
- History of laser treatment (including photodynamic therapy) to the macula for the study eye.
- History of intraocular surgery within 90 days for the study eye.
- History of anterior segment laser (laser peripheral iridotomy, laser to trabecular meshwork, YAG capsulotomy) within 90 days for the study eye.
- Media opacity (corneal scar, cataract) that would prevent adequate fundus imaging for the study eye.
- Any history of participation in another therapeutic clinical trial for GA.
- Participation currently or within the past 30 days in another therapeutic clinical trial in which a systemic or ocular study medication is received by the subject.
- GA in the study eye due to a cause other than AMD
- History of prior use of ALA.
- AREDS (Age Related Eye Disease Study) vitamins taken at standard doses are not considered an exclusion criterion. Taking any of the individual components of the AREDS vitamins at doses consistent with the AREDS formula (instead of taking the AREDS vitamins) is not considered an exclusion criterion. Taking a standard multivitamin is not considered an exclusion criterion. However, the multivitamin should not contain alpha lipoic acid (also known as thioctic acid).
- Taking antioxidant supplements other than a standard multivitamin (such as bilberry, vitamin C that is not part of a multivitamin or taken at higher doses than the AREDS formula, vitamin E that is not part of a multivitamin or taken at higher doses than the AREDS formula, or other similar antioxidants) within one month of enrollment is an exclusion criteria; these patients should discontinue the antioxidant supplement one month before enrollment in order to participate. Taking a supplement that has antioxidant potential that is recommended by a physician as standard-of-care medical management is not an exclusion criterion.
- Participant has a condition that, in the opinion of the investigator, would preclude participation in the study for 18 months (e.g., unstable medical status including blood pressure and glycemic control, unstable psychiatric history, moving and not able to return for all planned study visits).
- History of a formal diagnosis of dementia by a neurologist.
- History of gastric ulcer within the past 5 years.
- History of irritable bowel syndrome within the past 5 years.

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- History of severe, chronic gastric reflux such that it causes discomfort several times a week (within the past 6 months).
- Male subjects who refuse to use acceptable contraceptive methods.

4.2.3 Subject Recruitment

Subjects will be recruited from the investigators' clinical practice as well as from referring clinical practices on site. We may plan to utilize Penn media services to increase subject recruitment.

4.2.4 Duration of Study Participation

Subjects will participate in the study for an 18 month period (from the time of randomization).

4.2.5 Total Number of Subjects and Sites

Recruitment for screening visits will end after 50 subjects are randomized. If there are subjects that were already screened and consented at the time the 50th subject is randomized, then eligible patients will be allowed to proceed to the Run-In period and randomization (if the subject passes the Run-In requirements). This would not be expected to be more than a few subjects. It is expected that approximately 10-15 subjects per site will be enrolled in order to produce 50 evaluable subjects.

4.2.6 Vulnerable Populations

No vulnerable populations will be involved with this study.

5 Study Intervention

Please refer to sections 6.2.

5.1 Description of study medication

Study medication is comprised of ALA 600mg capsules or placebo capsules.

5.2 Intervention Regimen

Subjects will take one 600mg capsule of ALA (or placebo) once daily with a meal for 2 weeks and then increase to two 600 mg capsules of ALA (or placebo) once daily with a meal for the remainder of the 18 month period of the study.

For the tolerability test (Phase 1), see section 3.1.1. The 800 mg oral ALA dose will consist of two 400 mg capsules of ALA.

5.3 Receipt

The ALA is provided by Pure Encapsulations (Sudbury, MA). It is received, stored, handled, and distributed to investigators by the University of Pennsylvania Investigational Drug Service.

5.4 Storage

Active and placebo capsules will be stored, labeled and distributed to Investigators or directly mailed to the subject's home by the University of Pennsylvania Investigational Drug Service. All drugs (active drug and placebo) must be stored at room temperature.

5.5 Preparation and Packaging

In order to maintain the study blind, the Perelman School of Medicine Investigational Drug Service (IDS) will manufacture a placebo capsule to match the active ALA 600mg capsule provided by Pure Encapsulations Inc. A white, semi-opaque Size 0 pharmaceutical grade capsule shell will be filled with a combination of microcrystalline cellulose NF (approximately 600mg) plus trace amounts of coloring agents in order to closely mimic the appearance of the powder inside the active ALA capsule. Both placebo and ALA will be light yellow.

For dispensing, capsules will be hand-counted and placed into white opaque Type 2 HDPE

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pharmaceutical rounds which comply with USP<671> specifications, in either 120mL or 250mL capacity, with a PS-22 tamper-evident liner and a child-resistant cap. A non-child-resistant cap may be provided to the clinician on request, for the subject to switch to after dispensing if he/she has difficulty opening bottles and has no young children living at home. Bottles will include labeling compliant with FDA regulation, 21 CFR 312.6.

5.6 Blinding

Blinding only applies to Phase 2 of this protocol. A master file of subject assignments will be kept by the data coordinating center. The research team and the subject will be blinded and will not know the investigational product contained each capsule. The blind may be broken in the case of an emergency.

5.7 Administration and Accountability

When dispensing bottles of study run-in capsules, a member of the study team will record information onto the drug inventory logs. The Investigational Drug Service provides an “ALA for GA Study Medication Ordering, Distribution, and Accountability Manual” to each clinical center. Outdated supplies will be recalled by the Investigational Drug Service or destroyed on site and replacement supplies provided.

At each visit after the baseline visit and when run-in bottles are returned, unused study drug will be collected. Returned drug must be stored in the returned bottle in a secured location. The date the bottles are returned are noted on a drug accountability log.

All drug storage facilities and medication dispensing and collection records will be made available for inspection.

5.8 Subject Compliance Monitoring

Each Investigator must make visits as pleasant as possible by minimizing wait time and providing comfortable waiting and examination facilities. The Investigator for each Clinical Center will continually educate the subjects as to the nature of the study, the need for the subject’s continued participation, and answer questions concerning geographic atrophy and the use of ALA.

In Phase 2, subjects will be contacted to remind them of a follow up visit within the week of the appointment. The contact can be by telephone or email and a subject response is necessary. To ensure subject compliance for scheduled visits, early morning, evening, or weekend hours may be provided. Every effort must be made by the Investigator to remain in contact with subjects, even if they do not want to return to be examined or follow the protocol. After subjects enrolled in Phase 2 are randomized, they will be contacted at week 2 and months 1, 3, 9, and 15 months to ensure study drug compliance and to inquire about any difficulties with the study drug.

If a subject cannot tolerate the study medication (ALA or placebo) because of gastric reflux or symptoms thought to be from gastric reflux, they will be encouraged to prevent their symptoms by taking an over-the-counter gastrointestinal medication for reflux such as ranitidine or omeprazole. The investigator will make the determination that the symptoms are consistent with reflux and make the recommendation for gastrointestinal prophylaxis on a case-by-case basis. The investigator may choose to involve an internist in making this decision. Any use of gastrointestinal prophylaxis medications will be recorded. If ranitidine is desired to treat such symptoms at no cost to the subject because of reflux presumed to be related to the study medication, then a prescription may be sent (fax/email) to the UPenn IDS and the ranitidine will be mailed to the subject. The study’s Clinical and Scientific Expert must be notified and approve of this action within one week and prior to sending the ranitidine prescription to the Penn IDS.

If a subject cannot tolerate the study medication (ALA or placebo) for the reasons detailed below, then the subject will be asked if he/she is willing to take one capsule twice daily instead of two capsules once daily:

- there are uncomfortable gastrointestinal symptoms that do not resolve with medication for reflux,
- there are gastrointestinal symptoms and the subject does not want to take any prophylactic gastrointestinal medication, or

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- there are other symptoms causing intolerance of the study dose

If the subject cannot tolerate or does not want to take one capsule twice daily, then the subject will be asked if he/she is willing to take one capsule once daily. If the subject cannot tolerate one capsule once daily or does not want to take one capsule once daily, then the subject will be asked to at least remain in the study. All changes to the schedule of study medication dosing will be documented.

The study subjects will be asked to provide urine samples at the 12 months study visit. The urine will be tested for a metabolite of ALA to determine the subject's compliance. The samples will be tested in the Metabolomic Core Laboratory directed by Dr. Itzhak Nissim at the Children's Hospital of Philadelphia (CHOP). Please follow the instructions below for shipping of urine samples from each site to the Scheie Eye Institute lab for storage before analysis.

Instructions for shipping and handling of urine analysis samples:

Samples must be frozen (in a -20 °C freezer, shipping labels will be provided, samples must be shipped frozen on dry ice via overnight carrier to:

Dr. Josh Dunaief Laboratory
University of Pennsylvania
305B Stellar Chance
422 Curie Blvd
Philadelphia, PA 19104

Contact Information:

Office: 215-898-5235

Email: jdunaief@pennmedicine.upenn.edu

Urine samples will be stored in a freezer in the Dunaief Laboratory at -20 °C or less. The temperature of this freezer should not drop below -20 °C.

The collected urine samples will be transferred on dry ice to:

The Children's Hospital of Philadelphia (CHOP) Abramson Research Center (ARC) 5TH Floor,
Lab # 515 (A-D), 513 Metabolomic Core
3615 Civic Center Boulevard
Philadelphia, PA 19104-4318, USA

Contact information:

Ilana Nissim,

Email: NISSIMI@email.chop.edu

Tel: 215 590 3389

or

Evgueni Daikhin,

Email: DAIKHIN@email.chop.edu

Tel: 215 590 1675

ssitz@mail.med.upenn.edu

For questions please contact:

Itzhak Nissim, Ph.D

Metabolomic Core Director

Email: Nissim@email.chop.edu

The samples will be transferred from the Dunaief lab to the Nissim lab in a total 2-3 batches with the first batch sent after 35% or more of samples have been collected.

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5.8.1 Return or Destruction of Investigational Product

Completion of the study is met when a study subject completes the follow-up visits as specified by the subject's allotted study Phase. At this point, all remaining study medication will be collected. The amount of remaining capsules (if any) will be counted by study team personnel and reported to the coordinating center. The remaining study medication will be disposed of at the clinical site.

6 Study Procedures, Phase 1

6.1 Screening

At the baseline screening visit, a complete medical history list will be elicited from the subject and extracted from available medical records. Data to be collected include: age, gender, ethnicity, medical history, medications, allergies, ocular diseases, ocular surgeries, and non-ocular surgeries. A blood pressure and pulse will also be checked and documented at this visit. Based on all of this data, it will be confirmed that the patient meets all inclusion and exclusion criteria.

After signing the informed consent document, the ALA will be dispensed to the subject. Data will be directly collected onto case report forms, which will be considered the source data.

6.2 Study Intervention and Follow-up Phase

15 subjects (ages 65-90) will take 600 mg of oral ALA once daily with a meal for 5 days. This medication will be placed in a red-banded medication bottle (#1) with clear instructions. Each subject will be monitored by the study physician, who will record a history of any side effects or tolerability issues, including a complete review of systems. If well-tolerated, each subject will then take 800 mg of oral ALA once daily with a meal for 5 days. This medication will be placed in a green-banded medication bottle (#2) with clear instructions. Each subject will be monitored by the study physician who will record a history of any side effects or tolerability issues, including a complete review of systems. If 800 mg of oral ALA is well-tolerated, then these subjects will be asked to take 1200 mg of oral ALA daily again for 5 days with a concurrent meal. This medication will be placed in a blue-banded medication bottle (#3) with clear instructions. Each of these subjects will be monitored by the study physician who will record a history of any side effects or tolerability issues, including a complete review of systems. Patients will be contacted by the study physician every 5 days to check on tolerability issues and to determine if the patient can safely proceed to the next dose of ALA.

6.3 End of Study

At the time of the final phone call, the subject will be asked to discontinue the ALA. A final review of systems will be recorded. If there are no urgent issues, then the subjects will be asked to maintain continued care with their primary care physician and ophthalmologist.

The enrolled subjects will be provided an envelope (with postage cost already paid). This envelope will be mailed to the subject's home or given to him/her at the time of their enrollment visit. Using the envelope, the subject will be asked to mail all of the study medication bottles to the Scheie Eye Institute. There will be documentation of the received medication bottles and the amount of any unused study medication within them. Unused study medication will then be destroyed at the Scheie Eye Institute.

6.4 Unscheduled Visits

Unscheduled visits will be handled as typical standard of care visits by the treating ophthalmologist. Any exams and tests at unscheduled visits will be billed to the subject's insurance per the usual practices of that ophthalmologist. At the next scheduled study phone call, any adverse events related to the need for the unscheduled visits will be recorded. If there is a significant change in exam or a new diagnosis noted at the time of the unscheduled visit (i.e. new choroidal neovascularization, retinal vein or artery occlusion, vitreous hemorrhage, etc.) the Sponsor will be notified.

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6.5 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to other concerns. The Investigator or the Sponsor may withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

The enrolled subjects will be provided an envelope (with postage cost already paid). This envelope will be mailed to the subject's home or given to him/her at the time of their enrollment visit. In the event of subject withdrawal, the subject will be asked to mail all of the study medication bottles to the Scheie Eye Institute using the provided envelope. There will be documentation of the received medication bottles and the amount of any unused study medication within them. Unused study medication will then be destroyed at the Scheie Eye Institute.

7 Study Procedures, Phase 2

	Baseline Visit	6 months visit	12 months visit	18 months visit
EVA/ETDRS Refraction	X	X	X	X
Distance Corrected Near Visual Acuity (ETDRS)	X	X	X	X
Dilated Exam	X	X	X	X
Fundus Photos	X	X	X	X
Autofluorescence	X	X	X	X
OCT	X	X	X	X
Pulse, BP, BW	X	X	X	X
Urine Test			X	
Medical Review	X	X	X	X
Ocular Surface Disease Index	X	X	X	X

7.1 Screening (at baseline)

At the baseline screening visit, the informed consent document is signed by the subject. A complete medical history list will be elicited from the subject and extracted from available medical records. Data to be collected include: age, gender, ethnicity, medical history, medications, allergies, ocular diseases, ocular surgeries, and non-ocular surgeries. The subject will be given the option of completing the Ocular Surface Disease Index (OSDI).⁴⁷ A dilated eye examination will be performed. A blood pressure, pulse, and body weight will also be checked and documented at the baseline, 6 month, 12 month, and 18 month visit as part of a routine safety assessment. Based on all of this data, it will be confirmed that the subject meets inclusion and exclusion criteria.

Run-In Period: The subject will be mailed a medication bottle with the instructions to take one capsule once daily for 10 days and a form to record the starting and stopping dates. The medication bottle will contain the placebo but the subject will not be informed that the medication bottle contains placebo or ALA. After taking the capsule for 10 days, the subject will mail the medication bottle, including any remaining capsules, and form back to the clinical site using a postage-paid envelope provided at the time of the baseline screening visit. Those subjects that have demonstrated compliance by taking $\geq 80\%$ of the provided capsules and mailing the medication bottle within 40 days of the screening visit will now have met all inclusion and exclusion criteria. The subject will then be randomized and study medication will be mailed to the subject by the Penn IDS (see section 3.1.1 Allocation to Intervention Group). If an investigator did not receive a mailed medication bottle but believes the subject followed instructions and the medication bottle was lost in the mail, then that subject may get screened again for the study. In this instance, the subject will have to repeat the screening visit and the run-in period.

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Subjects that participated in the Run-In but did not demonstrate an ability to take $\geq 80\%$ of the capsules will be notified within two weeks that they cannot continue in the study and that they received placebo capsules during the Run-In. Subjects that continue to randomization will be informed after the study is completed that they received placebo capsules for the Run-In and whether they were randomized to placebo or ALA.

After signing the informed consent document and within 45 days before study treatment administration, all screening procedures, including OCT, FAF, fundus photography, BCVA, and the 10 day run-in phase must be performed.

Data will be directly collected onto case report forms, which will be considered the source data. There is no restriction on the number of subjects to be enrolled by a particular site.

7.2 Study Intervention Phase

7.2.1 6 Month, 12 Month, and 18 Month Visits

Fundus photographs, OCT and FAF images will all be collected at enrollment (baseline), 6, 12, and 18 month visits only. Both eyes will be imaged. These will be collected by ophthalmic photographers certified for clinical trial imaging. The Scheie Eye Institute Reading Center will provide detailed grading of FAFs, color fundus photographs, and OCTs for determination of study outcomes. Color fundus photographs, FAF and OCT images will be submitted to the Scheie Image Reading Center at enrollment (baseline), 6, 12, and 18 months. At each of these visits, the subject will be given the option of completing the Ocular Surface Disease Index (OSDI).⁴⁷

Study visits must fit the recommended time frame as much as possible. All follow-up study visits must at least be within 3 months (+/- 3 months) of the recommended date of the study visit.

7.2.2 Ophthalmic Procedures

Best-Corrected Visual Acuity (BCVA)/Refraction (Distance Measurement)

BCVA measurement should be performed on both eyes using the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol.⁴⁸ These will be performed by a study certified examiner. Traditional ETDRS charts may be used if the E-ETDRS chart is not available. BCVA and refraction will be done via protocol by a study certified examiner.

Best Distance-Corrected Near Visual Acuity (Near Measurement)

In order to evaluate the potential of ALA to improve presbyopia, a distance-corrected near visual acuity will be measured with a near vision ETDRS style chart. Using the distance correction (based on refraction), the near visual acuity will be measured for each eye with the near vision chart held at 16 inches (40 cm). This should be done regardless of the eye being phakic or pseudophakic.

Ophthalmoscopic Examination

Intraocular pressures (IOP) will be measured at each study visit. Pupils will be dilated with two sets each of 2.5% Neo-Synephrine and 1% Mydracyl, or equivalent. A complete anterior and posterior segment slit lamp exam will be performed by the study certified ophthalmologist including a lens assessment. This will be done with both a slit lamp and dilated ophthalmoscopy.

7.2.3 Photography

Keratometry

Automated or manual keratometry measurements will be made at the baseline screening visit. The corneal radius of curvature for each eye of each subject will be entered into the Heidelberg Spectralis machine. From the keratometry measurements, the average keratometry reading (K) for each eye is calculated $[(K1 + K2)/2]$. Then, the corneal radius of curvature (mm) can be calculated using the formula

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and the average K measurement: $r = 337.5/K$. Keratometry measurements will be re-measured and updated within the Spectralis if a subject has had any ophthalmic surgery or history of corneal suture removal since the last study visit.

Fundus Photography

A photographic field between 30 and 40 degrees is required. Stereo color photographs of standard fields 1, 2 and modified 3 will be obtained. Photographs from baseline, months 6, 12, and 18 will be read by the Scheie Image Reading Center for an independent assessment. Fundus photos should be acquired before fundus autofluorescence images are acquired.

Spectral Domain Optical Coherence Tomography (OCT)

All OCT images from enrollment (baseline) and months 6, 12, and 18 months will be read by the Scheie Image Reading Center for additional outcomes. These images will be acquired with the Heidelberg Spectralis (Carlsbad, CA).

Fundus Autofluorescence (FAF)

The areas of geographic atrophy will be evaluated from FAF images taken with the Heidelberg Spectralis (Carlsbad, CA) using the Blue Peak Blue Laser Autofluorescence mode. The FAF images should be taken after the color fundus photos and OCT imaging.

All FAF images from enrollment (baseline) and months 6, 12, and 18 will be read by the Scheie Image Reading Center.

Geographic Atrophy

Geographic atrophy (GA) will be assessed from the color fundus photographs and FAF images. On color photographs, GA is observed as one or more sharply defined, more or less circular patches of absence of the RPE, typically with exposure of underlying large choroidal blood vessels. At a minimum, at least two of the aforementioned characteristics (sharp edges, more or less circular shape and visibility of underlying choroidal vessels) with a minimum size of ≥ 175 microns in longest linear dimension are required for a lesion to be categorized as GA.⁴⁹ While a minimum size of ≥ 175 microns in longest linear dimension is required for a lesion to be categorized as GA for grading once an eye is in the study, the GA size requirements for study eye inclusion stated in section 4.2.1 (Inclusion Criteria) still stand.

Once geographic atrophy has been identified on the color photographs and FAF by the grader, the grader will use the Region Finder semi-automated software of the Heidelberg Spectralis to measure the areas of geographic atrophy at the macula of the study eye. While the color photographs are used to categorize a lesion as GA, the primary measure of GA area will be taken from the FAF images. The color photos can also be used to assist in the interpretation of the FAF images. GA appears as well defined hypoautofluorescent patches in FAF images. All areas of GA at the macula of the study eye will be measured.

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7.3 Follow Up Phase of the Study

7.3.1 End of Study Visit

Two weeks following the 18 months visit, the subject will be contacted to determine if there have been any adverse events following the completion of the study and to ensure that the subject has a follow-up eye examination (outside of the study) with an ophthalmologist.

7.4 Unscheduled Visits

Unscheduled visits will be handled as typical standard of care visits by the treating ophthalmologist. Any exams and tests at unscheduled visits will be billed to the subject's insurance per the usual practices of that ophthalmologist. At the next scheduled study visit, any adverse events related to the need for the unscheduled visits will be recorded. If there is a significant change in exam or a new diagnosis noted at the time of the unscheduled visit (i.e. new choroidal neovascularization, retinal vein or artery occlusion, vitreous hemorrhage, etc.), the Sponsor will be notified

7.5 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to other concerns. The Investigator or the Sponsor may withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who wish to withdraw early will be asked to have one final visit to collect investigational product and to follow up regarding adverse events before formal withdrawal of consent.

7.5.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who wish to withdraw consent to participate in the study will be asked to have one final visit to collect the investigational product. During this visit they will be asked for permission to have the study team look into their survival status via publically available means.

7.6 Early Termination Visits

If a subject terminates the study early, a follow-up visit will be scheduled to assess subject safety and collect unused drug. The reason for early termination will be recorded on the case report form. AEs and SAEs will be recorded. The Investigator will ensure that the subject has a follow-up standard-of-care visit scheduled with an ophthalmologist for their continued eye care.

8 Statistical Plan

8.1 Primary Endpoint

For Phase 1 of this protocol, the primary endpoint is the percent of adverse events that develop in the study group at each studied dose of ALA.

For Phase 2 of this protocol, the primary endpoint is the mean rate of change of the area of GA in the study eye from baseline to 18 months (from the time of randomization) as evaluated by fundus autofluorescence.

8.2 Secondary Endpoints

A secondary endpoint for Phase I is the percent of subjects that think they could tolerate each studied dose of ALA for a duration of 18 months. If 4 or more (out of 15) subjects state that they could not imagine taking a particular dose for 18 months, then that dose will not be used in the Phase 2 Trial.

The secondary endpoints for Phase 2 include:

- The change in best corrected visual acuity (BCVA) from baseline to 18 months from the time of randomization

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- The proportion of subjects with three lines or more worsening in BCVA
 - Absolute and relative change in area of GA as measured on FAF
 - Rate of change over time (18 months from the time of randomization) in area of GA in the study eye as measured on color fundus photos.
 - Absolute and relative change in area of GA as measured on color fundus photos
 - Change in drusen volume based on OCT and change in the number of drusen seen on color fundus photos (exploratory endpoint)
 - Change in score on the Ocular Surface Disease Index (OSDI)⁴⁷ (exploratory endpoint)
 - Change in best distance corrected near visual acuity (exploratory endpoint)
- Ocular and systemic safety outcomes for these doses of ALA

8.3 Sample Size and Power Determination

Phase 1: It is expected that a sample size of 15 subjects will adequately determine if there is a significant intolerance of the tested doses of ALA in the elderly population.

Phase 2: In addition to assessing the safety profile of ALA and the feasibility of study procedures, one of the major goals of the proposed study is to determine if additional, larger scale assessments of efficacy are warranted. For pilot studies, it is appropriate to use a confidence interval approach to evaluate outcomes and pre-specify a clinically important threshold to determine if further investigation is justified.⁵⁰⁻⁵¹ If we decide to halt investigation if the observed growth rate in the actively treated group is greater than in the placebo group, then it is reasonable to use a one-sided confidence interval. With 50 total subjects, we can be 90% confident (one-sided) that the “effect size” of ALA in reducing the GA growth rate is 0.4 or less. This number assumes that 15% of subjects dropout. An example of an effect size of 0.4 would be a growth rate of 0.40 mm in the placebo group and a growth rate of 0.32 (20% reduction) in the ALA group when the standard deviation of the annual growth rate is 0.20 mm.⁵² Interventions with less efficacy than this may not be worth pursuing.

Based on current data, it is possible that approximately 25% of subjects randomized to the ALA arm may not tolerate 1200 mg of ALA. Instead of 1200 mg once daily of ALA, some of these patients may elect to take 600 mg twice daily or 600 mg once daily. An intention to treat analysis will be performed on all subjects randomized to 1200 mg ALA in comparison to the placebo group. Subgroup analyses will be performed on those subjects remaining at 1200 mg and subjects at a lower dose of ALA. After 25 subjects have enrolled in the study, we will perform interim analyses of the numbers of subjects in these subgroups without evaluating any outcomes data. Depending on the status of enrollment, drop-out rates, and the size of the subgroup consistently taking 1200 mg subgroup, the study sample size may be increased at this time so that the 1200 mg subgroup has a number equal to or nearly equal to 22 subjects available for analyses.

8.4 Statistical Methods

Phase 1: Percentages of adverse events will be calculated.

Phase 2: As a preliminary analysis, the mean change in the total area of GA within study eyes over 18 months (from the time of randomization) will be compared between eyes receiving the active ALA dose and placebo supplementation; a square root transformation will be applied to the area measurements to mitigate the dependence of growth rate on initial size.⁵³⁻⁵⁴ Also, mean change in visual acuity over 18 months, the proportion with a decrease of 15 letters (3 lines) of visual acuity, and the proportions with serious adverse events will also be compared. Variants of the independent t-test and chi-square tests of proportions that account for the correlation between eyes of subjects who have two study eyes will be used to make comparisons.

The main analysis for comparing treatment groups will compare the rates of change in total area of GA using a mixed effects linear model. Use of this model allows including all patients in the analysis and requires less stringent assumptions than a complete cases analysis regarding the association of

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missingness with the outcome variable and does not introduce bias into the estimation of the slope parameter as a “last observation carried forward (LOCF)” approach does when area changes with time. Both subject and eye will be considered random effects. A sensitivity analysis using multiple imputation for missing values will be used for the analysis of mean change between baseline and 18 months and for the mixed effects linear model of total area.

Similar analytic methods using mixed effects models will be used for the other outcome measures.

8.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

8.4.2 Safety Analysis

Phase 1: All subjects entered into the study will have detailed information collected on adverse events for the overall study safety analysis. Symptoms reported will be graded as mild, moderate, or severe in nature.

Phase 2: All subjects entered into the study and randomized at the baseline visit will have detailed information collected on adverse events for the overall study safety analysis

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with new clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Example, loss of 6 lines of visual acuity on the ETDRS chart
- A congenital anomaly or birth defect

9.2 Recording of Adverse Events

At each contact with a subject, an Investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report

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form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though they should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

Principal Investigators will determine the relationship of each adverse event to the study procedures or study drug. The relationship will be classified as any of the following:

- Definitely related
- Probably related
- Possibly related
- Unlikely or unrelated

9.4 Reporting of Adverse Events and Unanticipated Problems

The Data Coordinating Center receives notification of Serious Adverse Events (SAEs) via a specific form completed by the investigator and submitted within 24 hours. An assessment of all incoming SAEs is made to determine whether the event needs to be reported to the FDA. The Coordinating Center sends an electronic copy of each Serious Adverse Event Report Form, as well as baseline medical history, medications reported at baseline and follow-up, and other supporting documentation as needed to the Sponsor within 24 hours. The Coordinating Center also sends all AEs to the Sponsor. All SAEs are reviewed by the Sponsor as required by regulation.

9.4.1 Investigator reporting: notifying the study sponsor

Any serious adverse event will be reported to the study Sponsor within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the Investigator and sent to the Sponsor, via the Data Coordinating Center, within 24 hours. The Investigator will keep a copy of each SAE form on file at the study site. Report serious adverse events to:

Clinical Trials Coordinating Center
Center for Preventive Ophthalmology and Biostatistics
3535 Market Street Suite 700
Philadelphia, PA. 19104-3309
215-615-1505
215-615-1531 (fax)

Within the following 24 hours, the Investigator will provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form and any other information that will assist the understanding of the event. Significant new information for ongoing serious adverse events should be provided promptly to the study sponsor.

9.4.2 Investigator Reporting: Notifying the local IRB

Each Principal Investigator will follow his/her IRB's reporting requirements. The University of Pennsylvania Investigator will report AEs at least annually to the University of Pennsylvania IRB. Investigators will promptly report any unexpected and related AEs to the IRB, including suspected adverse reactions. Other prompt reporting requirements will include: changes, violation, or deviation to the protocol without prior IRB and Sponsor review to eliminate immediate hazard to a study subject, complaint of a subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team, breach of confidentiality, and premature completion of the study. For the UPenn site, an unanticipated problem that includes risk to other subjects must be reported to the IRB within 10

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working days. If an SAE involves death and other subjects are at risk, the UPenn Investigator must submit a report to the UPenn IRB within 3 days.

9.4.3 Sponsor reporting: Notifying the FDA

This protocol is being conducted under an FDA IND. The Sponsor will report all adverse events to the FDA in the Annual Report and all unanticipated, related and serious adverse events to the FDA per regulation.

9.4.4 Sponsor reporting: Notifying participating investigators

In addition to reporting to the FDA, the Sponsor shares SAEs with participating Investigators.

9.5 Unblinding Procedures

The unblinding of the research team will only be performed if there is an emergency or time-sensitive event for which unblinding would help manage the event. In this case, the Coordinating Center will provide documentation of whether the subject received placebo or ALA within 24 hours of the request to the Coordinating Center. If possible, the study subject will remain blinded. However, if deemed necessary and appropriate by both the site investigator and the Sponsor, the subject can be provided documentation of whether he/she received placebo or ALA within 24 hours of this request.

9.6 Monitoring

9.6.1 Data and Safety Monitoring Plan

Phase 1: After a subject has taken a study dose for 5 days, a study physician will contact the subject and do a complete review of systems to document any adverse events. Symptoms reported will be graded as mild, moderate, or severe and this data will be recorded. If a subject does not feel comfortable proceeding to the next higher dose, then that subject will stop participation in the study at that point. If after review of the adverse event(s) (and their quality) that a subject experienced at a particular dose, then the study physician also may stop the subject's participation in the study if there is any safety concern. If 4 or more (out of 15) subjects state that they could not imagine taking a particular dose for 18 months, then that dose will not be used in the Phase 2 Trial. Adverse events, the severity of adverse events, and the percent of subjects that think they could take a particular dose of ALA for 18 months will be reported to the University of Pennsylvania IRB before proceeding with Phase 2. A Data and Safety Monitor (DSM) will also independently review all adverse events as outlined in the DSM Charter.

Phase 2: While each Principal Investigator has safety oversight of the study conducted at their site, there will also be a Data and Safety Monitor (DSM). Review of known risks from ALA has suggested that ALA is relatively safe and well tolerated (see Section 1.2.2). A Drug Safety Monitoring Plan has been developed based on risk.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain

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permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Phase 1: For the ALA tolerability test, data will be entered onto case report forms by the Research Coordinator or Physician Investigator. There will be no electronic records for the tolerability test.

Phase 2: Data will be directly collected onto case report forms in real time by the study-certified clinic coordinator or examining ophthalmologist. The case report forms will be considered the source data. Data will be entered by study certified clinic coordinators into a central database using the Research Electronic Data Capture (REDCap) system.⁵⁵ REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Clinical examination data are recorded directly onto the CRFs during the clinic visit and are considered the source documentation. Each item entered by the clinic coordinator is checked for valid codes, legitimate ranges, legal dates, etc. and invalid entries are flagged. Validation of data occurs during and after the data entry session. Electronic logs of the completion status of each form and assessment are tracked by the Coordinating Center to determine the status of data collection for each registered participant. Form revisions and additions are accommodated by having data management staff at the Sponsor modify or create the appropriate data definition.

Data that have been entered into REDCap are subject to additional consistency checking involving more complex logic than implemented during data entry checking. Often these post-entry checks involve several different forms and visits. The Center for Preventive Ophthalmology and Biostatistics (CPOB) biostatistician will develop the logic for these checks and the comments to be associated with the resulting data queries. The Clinic Coordinator reviews edit messages and the corresponding data forms. If necessary, the Clinic Coordinator corrects the paper form, initials and dates the form, and updates the online database. The updated data records are again subjected to the entire data checking system. When extraordinary circumstances arise in which the query may never be able to be resolved to meet the requirements of the edit logic, the biostatistician may, with the approval of the Director, flag specific items on specific forms as exempt from further edit. The REDCap system generates an entry into a log of changes after every record correction so that a fully verifiable audit trail is created.

Records Retention

REDCap databases are backed up on a regularly scheduled basis. The backup data files are kept in a secured environment and are available for recovery. Data files that reside on the CPOB file server are backed up nightly. In addition, all CPOB personnel are required to keep copies of key documents such as forms, correspondence, and reports on the file server, which is on an automatic backup schedule. Files of the data system as of the time of each data freeze and for each publication are also archived.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

Phase 1: After a subject has taken a study dose for 5 days, a study physician will contact the subject and do a complete review of systems to document any adverse events. Symptoms reported will be graded as mild, moderate, or severe and this data will be recorded. If a subject does not feel comfortable proceeding to the next higher dose, then that subject will stop participation in the study at that point. If after review of the adverse event(s) (and their quality) that a subject experienced at a particular dose, then the study physician also may stop the subject's participation in the study if there is any safety concern. If 4 or more (out of 15) subjects state that they could not imagine taking a particular dose for 18 months, then that dose will not be used in the Phase 2 Trial.

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Phase 2: Both the Sponsor and the Principal Investigators ensure safety and compliance. There will be a Data and Safety Monitor (DSM). A Data Safety Monitoring Plan has been developed based on risk. At this time there is no Data Safety Monitoring Board as this is low risk study.

The Investigators will allocate adequate time for monitoring with regards to accurate and confidential record keeping, appropriate reporting of adverse events by all sites, The investigators will ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB, the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12 Ethical Considerations

This study is to be conducted in accordance with applicable US regulations, international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

The protocol and any amendments will be submitted by each PI to his/her Institutional Review Board (IRB). The decision of the IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of each decision will be provided to the Sponsor before changes are implemented in the study.

12.1 Risks

Risks of Eye Examination Procedures and Tests

There is a very rare risk of an allergic response to the topical medications used to anesthetize the eye (for eye pressure measurement) or dilate the pupil. This occurs in less than 1% of eyes. Dilating drops rarely could cause an acute angle closure glaucoma attack (less than 1 in 1000).⁵⁶

There are no known risks associated with OSDI survey, OCT, autofluorescence, or fundus photographs.

Risks of study investigational medicines: Alpha Lipoic Acid (ALA) and placebo

ALA and placebo study drug risk is low. ALA is available over-the-counter and is approved in Germany for the treatment of diabetic peripheral neuropathy.⁵⁻⁸ The safety of ALA has been extensively evaluated. ALA is metabolized by the liver and is known to be safe in both hepatic and renal disease. The primary side effects from oral ALA are gastrointestinal and occur at doses of 1200 mg or higher. These gastrointestinal side effects predominantly involve an upset stomach, gastric reflux, nausea, and can be minimized if ALA is taken in divided doses or with a meal, although concurrent food ingestion may partially reduce the bioavailability.³⁵⁻³⁷ There can also be a malodorous urine and headache. Rare complications that may be related to ALA included one patient who developed an allergic rash, fever, and mild thrombocytopenia that resolved after stopping ALA and reports of a rare occurrence of insulin autoimmune syndrome.³⁸⁻³⁹ Most of these published studies on the safety and tolerability of ALA at doses of 1200 mg or higher involve adults that are not elderly.

12.2 Benefits

A key benefit is believed to be a reduction in GA enlargement in patients with AMD. Our central hypothesis, based on the existing literature and our own preliminary data, is that oral lipoic acid supplementation reduces the rate of enlargement of GA in AMD patients. Subjects may not directly

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benefit from participation in this study. Nevertheless, subjects who participate in this study will receive medical care and monitoring. Furthermore, information from this study may help subjects and others with geographic atrophy secondary to AMD receive better care in the future.

Depending on funding availability, some subjects may be provided financial assistance with transportation costs at the discretion of the principal investigator.

Depending on funding availability, subjects may be provided a \$40 gift card at each of the follow-up study visits and a \$100 gift card at the final study visit.

For the tolerability test (Phase 1), it is not expected that subjects will receive any direct benefit. However, information from the tolerability test will help to confirm the dose chosen for the Randomized, double-blind placebo controlled trial (Phase 2).

12.3 Risk Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study as there is little risk of serious adverse events occurring and the potential benefit is a reduction of vision loss for participants.

For the tolerability test, there is unlikely to be any direct benefit to the subjects, but the risk of serious adverse events is considered low.

12.4 Informed Consent Process / HIPAA Authorization

Written informed consent must be obtained before any of the baseline procedures are performed. An explanation of the trial and discussion of the possible risks and discomforts will be given by the Investigators and/or study staff. Only those patients who fulfill all eligibility criteria will be entered into the trial. Informed consent will take place as an ongoing dialogue between the Investigator/study staff and subjects during the entire duration of their participation. Patients that are unable to read the study consent and/or do not have the opportunity to take home and review with family/friends or do not present in the clinic with a family member will have the consent read to them by a study team member in the presence of a non-partial person that will verify the consent has been read in full to the patient. Phase 1 and Phase 2 will have separate ICFs.

12.4.1.1 Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible per IRB SOPs)

No waiver requested.

12.4.1.2 Waiver of Written Documentation of Consent

No waiver requested.

12.4.1.3 Waiver of Written Documentation of Consent where the research is subject to FDA regulations

No waiver requested.

12.4.1.4 Waiver of HIPAA Authorization

No waiver requested.

13 Study Finances

13.1 Funding Source

This study is financed primarily through a grant from the Bright Focus Foundation. There is additional support provided by the Pennsylvania Lions Sight Conservation and Eye Research Foundation and the Scheie Eye Institute (University of Pennsylvania).

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This material is the property of the University of Pennsylvania.

13.2 Conflict of Interest

All Investigators will follow their University policies on conflict of interest. There are no subject payments or stipends.

14 Publication Plan

The primary responsibility for publication is held by the University of Pennsylvania study chair. Investigators that have contributed meaningfully to the project or have recruited a significant number of subjects will be involved in the manuscript preparation. Pure Encapsulations, Inc. (a subsidiary of Atrium Innovations Inc.) will be given the opportunity to review and comment on manuscripts prior to publication. Pure Encapsulations, Inc., may, at its sole discretion, request to be disclosed as the supplier of ALA in the “Materials and Methods” or some similar format when data are presented or published. Pure Encapsulations, Inc. may request that their company name or the ALA product name is disclosed in abstracts.

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16 Appendices

- Appendix 1, Sample Consent Form (Phase 2)
- Appendix 2, Sample Consent Form (Phase 1)

17 Additional Information

17.1 Expedited FDA Reporting Requirements

The Sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/ IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

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Within 7 calendar days

Any study event that is all:

- associated with the use of the study drug, and
- unexpected, and
- fatal or life-threatening,

Within 15 calendar days

Any study event that is:

- associated with the use of the study drug, and
- unexpected, and
- serious, but not fatal or life-threatening
- A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).
- Any finding from non-clinical studies that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Sponsor will assess all SAEs and perform an aggregate analysis on all AEs as per regulation.

Reporting Process

Applicable events will be reported to the FDA using [Form FDA3500A](#).

17.2 Source Documents (definition)

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

17.3 Case Report Forms (CRFs) (definition and guidelines)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE OR WHITE OUT ERRORS.** For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

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