

Phase 2a Study of the Effect of **Serine** Supplementation and **Fenofibrate** Treatment on Serum Deoxysphinganine Levels in Patients with Macular Telangiectasia (MacTel) Type 2 (SAFE Study)

Sponsor –The Lowy Medical Research Institute (LMRI), Ltd.

Level 19, 60 Martin Place

Sydney, New South Wales 2000 Australia

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Statement of Compliance

This study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to 45 CFR 46, 21 CFR 50, (Human Subjects Protection), and 21 CFR 56 (Institutional Review Board [IRB]) and CFR 312.2b.

1. INTRODUCTION

Table 1. Study Personnel

Lowy Medical Research Institute, Ltd. (LMRI) Sponsor L19 60 Martin Place Sydney, New South Wales, AU			
Katie Nardo MPH <i>Project Manager</i> 858-249-7013 office(US) knardo@lmri.net Primary Contact for all study related questions			
Contact for urgent or after-hours issues Jennifer Trombley RN MSN CCRC <i>Director, Clinical Operations, LMRI</i> 858.249.7109 office (US) 760.666.0452 mobile (US) jtrombley@lmri.net	Marin Gantner PhD <i>Staff Scientist, LMRI</i> 858.249.7104 office (US) mgantner@lmri.net	Martin Friedlander MD PhD <i>President, LMRI</i> 858.784.9138 office (US) friedlan@scripps.edu	Simone Tzaridis MD <i>Medical Monitor, LMRI</i> 858.249.7108 office (US) smueller@lmri.net

All questions should first be directed to the Project Manager.

2. EXECUTIVE SUMMARY

This document details the controlled Phase 2a study of the effect of serine supplementation and fenofibrate treatment on serum deoxysphingolipid levels in patients with macular telangiectasia type 2 (MacTel). This study involves six arms. Participants will be randomly assigned to one of the following treatment groups: serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, both serine 200 mg/kg/day and fenofibrate 160 mg/day, both serine 400 mg/kg/day and fenofibrate 160 mg/day, or no treatment (control group). Serum deoxysphingolipid levels will be

used as the primary outcome, and safety will be evaluated. The participants will be followed for 10 weeks, with visits at Screening, Week 0, 3, 6 and 10.

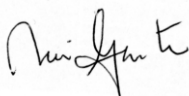
Due to the small number of participants per study treatment group enrolled in this study, the data will be analyzed by descriptive statistics.

SPONSOR SIGNATURE

The signatures below document the review and approval of this protocol and provide the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. Code of Federal Regulations and ICH guidelines.

Marin Gantner, PhD

Staff Scientist

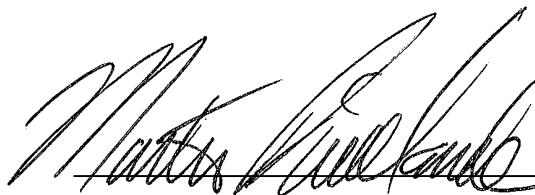
Sponsor Representative's Name (Print)_____
Sponsor Representative's Title

13JUN2022

Sponsor Representative's Signature_____
Date

Martin Friedlander, MD PhD

President

Sponsor Representative's Name (Print)_____
Sponsor Representative's Title

14JUN2022

Sponsor Representative's Signature_____
Date

SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and supporting documents from the sponsor and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol. I understand and am aware of my responsibilities as an investigator as described in the applicable GCP regulations.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the IRB/IEC responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, Part 312.64. This study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to 45 CFR 46, 21 CFR 50, (Human Subjects Protection), and 21 CFR 56 (Institutional Review Board [IRB]).

Principal Investigator Name (Print)

Principal Investigator Signature

Date

3. SYNOPSIS

1.1.	Phase 2a Study of the Effect of Serine Supplementation and Fenofibrate Treatment on Serum Deoxysphinganine Levels in Patients with Macular Telangiectasia (MacTel) Type 2
1.2. Clinical Phase	Phase 2a Study
1.3. Indication	Macular Telangiectasia Type 2
1.4. Study Objectives	
1.4.1. Primary Objectives	To evaluate changes in serum deoxysphingolipid levels within and between arms following treatment with: serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, both serine 200 mg/kg/day and fenofibrate 160 mg/day, both serine 400 mg/kg/day and fenofibrate 160 mg/day, or no treatment (control). To evaluate changes in blood chemistry and lipid levels as an indication of the safety of the treatment.
1.4.2. Secondary Objective	To evaluate changes in amino acid and lipid levels within and between arms following treatment with: serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, both serine 200 mg/kg/day and fenofibrate 160 mg/day, both serine 400 mg/kg/day and fenofibrate 160 mg/day, or no treatment (control).
1.5. Study Endpoints	
1.5.1. Primary Endpoints	Serum deoxysphingolipid, other lipid and amino acid levels
1.5.2. Secondary Endpoints	- Blood chemistry and lipoprotein (vLDL/LDL and HDL) levels - Gut microbiome analysis
1.6. Study Population	
A minimum of 60 and up to 120 male and female participants (10-20 participants per treatment group) with confirmed MacTel Type 2, aged 21 years or older. The study will be conducted at up to 10 clinical sites.	

1.7. Study Design

This is a multi-site, multi-arm, randomized, open-label Phase 2a study designed to evaluate the effect of serine supplementation and fenofibrate treatment on serum deoxysphingolipid levels in patients with macular telangiectasia (MacTel) type 2. This study involves six arms. Participants will be randomly assigned to one of the following treatment groups: serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, both serine 200 mg/kg/day and fenofibrate 160 mg/day, both serine 400 mg/kg/day and fenofibrate 160 mg/day, or no treatment (control group). Primary outcome measures are serum deoxysphingolipid levels and safety of treatment. Serum amino acid and lipid levels will also be evaluated. Gut microbiome samples will be collected and analyzed to determine if there is an interaction between the gut microbiome composition and the effects of the treatments. The participants will be followed for 10 weeks with visits at Screening, Weeks 0, 3, 6, and 10.

Up to 120 but no less than 60 participants will be enrolled. At the Screening visit (Week -1), study participants will have a BMI assessment and a fasting blood sample will be collected. Participant eligibility will be determined upon receipt of the Screening blood results. At the Baseline (Week 0) visit, participants will be randomized into their respective arms. The study team will dispense investigational product and review dosing instructions with the participants. Participants will continue treatment for six weeks, followed by a washout period of four weeks. Participants will return for a follow-up visit at the end of the wash-out period, at 10 weeks. At each follow-up visit a fasting blood sample will be collected.

1.8. Entry Criteria**1.8.1 Inclusion Criteria**

1. Signed and dated written informed consent obtained from the participant in accordance with the local regulations;
2. Males/females 21 years of age or older;
3. English speaking;
4. Enrolled in the Natural History Observation and Registry Study (NHOR) and diagnosed with confirmed MacTel type 2 in at least one eye;
5. Willing to use contraception, if applicable; and
6. Willing to comply with study protocol and follow-up visits.

1.8.2 Exclusion Criteria

1. Participant is unable to provide informed consent;
2. Participant is less than 21 years of age;
3. Participant is currently taking, or has taken within four weeks prior to screening, a serine or glycine supplement;
4. Participant is currently taking, or has taken within 12 months prior to screening, fibrates including clofibrate, ciprofibrate, bezafibrate, fenofibrate, and gemfibrozil;
5. Participant is currently taking an anticoagulant, colchicine, cyclosporine, tacrolimus or bile acid binding resins;
6. Participant has known allergy to fibrates and/or serine;
7. Participant has a known history of clinically significant myopathy or myalgia related to cholesterol-lowering drugs;
8. Participant has active liver disease and/or elevated liver enzymes*;
9. Participant has renal dysfunction as evidenced by elevated serum creatinine* and/ or glomerular filtration rate (GFR) less than 60 mL/min;
10. Participant has thrombocytopenia as evidenced by a platelet count below 100,000 per microliter, anemia as evidenced by hemoglobin levels below 10 g/dL, or history of bleeding disorder;
11. Participant has a history of gallbladder disease or has had a cholecystectomy;
12. Participant has triglyceride levels greater than 400 mg/dL on treatment, or greater than 700 mg/dL on no treatment;
13. Participant has untreated/uncured Hepatitis C, or a history of Hepatitis B, autoimmune hepatitis, or HIV;
14. Participant has had any malignancies within the last 5 years (not including basal cell carcinoma);
15. Participant has ever been enrolled in a clinical trial involving ciliary neurotrophic factor (CNTF) treatment;
16. Participant is currently enrolled in another clinical trial that involves treatment or participated in one within the last 30 days;
17. Participant is pregnant, breastfeeding or planning a pregnancy;
18. Participant is medically unable to comply with study procedures or follow-up visits;

19. Participant has, in the opinion of the Investigator, any physical or mental condition that would increase the patient's risk of participation in the study or may interfere with the study procedures, evaluations and outcome assessments; or

20. Patient is unavailable for follow-up visits.

**based on reference range for the local laboratory used*

1.8.1. Statistical Analysis

Due to the small number of participants per treatment group enrolled in this study, the data will be analysed by descriptive statistics.

Assessment/Examination Schedule

1. For women of childbearing potential

	Week -1 Visit 1	<i>before week 0</i>	Week 0 (+/-3 days) Visit 2	Week 3 (+/-3 days) Visit 3	<i>during week 5</i>	Week 6 (+/-3 days) Visit 4	<i>during week 9</i>	Week 10 (+/-3 days) Visit 5
GENERAL ASSESSMENTS	Screening		Begin treatment			Stop treatment		
Informed Study Consent	X							
Review Eligibility Criteria	X		X					
Demographics and Participant Contact Information	X							
Medical & Ophthalmic History	X							
AE Assessment – <i>starting from Week 0</i>			X	X		X		X
Concomitant Medications	X		X	X		X		X
Height and Weight for BMI Assessment	X							
Pregnancy Test ¹	X			X				
Ophthalmic Imaging: OCT			X					
Ophthalmic Imaging: Fundus Photo			X					
Gut Microbiome (Fecal) Sample Collection and Submission (x3 within each window of time) ²		X			X		X	
Fasting Blood Sample - Metabolites	X		X	X		X		X
Blood Sample - Chemistry/Lipid panel/Lipase/Creatine Phosphokinase/CBC with differential/HbA1c ³	X			X		X		X
Blood sample – Genetics ⁴	X							
Randomization & Begin Treatment (serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day AND fenofibrate 160 mg/day, serine 400 mg/kg/day AND fenofibrate 160 mg/day, or no treatment (control group))			X					
Stop Treatment						X		
Medication Compliance				X		X		

2. Participant collects at-home; if participant has strong aversion to microbiome sample collection, but otherwise meets eligibility criteria, they can still participate in the study

3. HbA1c only performed at the screening visit

4. If not previously collected at NHOR enrollment and participant consent

List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse event
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HSAN1	Hereditary Sensory and Autonomic Neuropathy Type 1
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MacTel	Macular telangiectasia type 2
NHOR	Natural History Observation and Registry Study
SAE	Serious adverse event

4. PRÉCIS

Macular telangiectasia type 2 (MacTel), an age-related bilateral degenerative condition of the macula that may cause progressive loss of vision, is estimated to have an incidence of 1:2,200 (Aung 2010, Klein 2010, Sallo 2012). Recent research by the MacTel Consortium has determined that MacTel patients have low serine levels compared to a matched control group, and that low serine is correlated with elevated deoxysphingolipids, which are toxic to neurons (Gantner 2019). The purpose of this study is to determine if and to what extent serine supplementation or fenofibrate treatment reduces circulating levels of deoxysphingolipids in MacTel patient serum. Fasted serum will be collected prior to, during, between and after supplementation/treatment to monitor deoxysphingolipid levels.

5. BACKGROUND AND RATIONALE

Macular telangiectasia type 2 is the most common form of macular telangiectasia, often referred to as “MacTel.” This condition is typically diagnosed in the fourth or fifth decade of life in both sexes. This disorder is characterized by minimal exudation, superficial retinal crystalline deposits, retinal opacification and right-angle venules. As the disease progresses, intraretinal pigment plaques and secondary neovascularization may develop.

MacTel has a complex genetic inheritance pattern and cannot be explained by any one or several genetic drivers. Despite the genetic complexity, MacTel patients share a common metabolic “phenotype.” A genome-wide association study combined with metabolic analysis of serum have identified that the MacTel patient population has reduced circulating serine levels (Scerri 2017). Serine is a non-essential amino acid crucial to mammalian cell metabolism. One of the key functions of serine is to generate sphingolipids necessary for cell function and signaling. When serine levels are low these lipids are synthesized from other amino acids. The resulting atypical lipids, deoxysphingolipids, have been shown to be toxic to many cell types including neurons (Duan 2015). These data suggest that increasing serine levels will reduce deoxysphingolipid levels and, by inference, neurotoxicity and associated neurological deficits.

The rare peripheral neuropathy, hereditary sensory and autonomic neuropathy type 1 (HSAN1), is caused by a genetic variant that elevates deoxysphingolipid levels (Eichler 2009). Interestingly, many of these patients also have MacTel, indicating that elevated deoxysphingolipids are a clear risk factor for MacTel (Gantner 2019). Furthermore, MacTel patients without HSAN1 also have elevated deoxysphingolipid levels as a consequence of their reduced

serine levels (Gantner 2019). We have shown that these deoxysphingolipids are toxic to photoreceptors in culture and may also be toxic in human eyes. These data suggest reducing deoxysphingolipid levels may benefit patient clinical outcomes.

6. SCIENTIFIC RATIONALE

It has previously been shown in HSAN1 patients that serine supplementation reduces serum deoxysphinganine levels (Garofalo 2011). This pilot study found that supplementation with both 200 and 400 mg/kg/day of serine dramatically reduced serum deoxysphingolipid levels, with the higher dose having a more profound and consistent impact (Garofalo 2011). Unlike HSAN1 patients, who have elevated deoxysphingolipid levels due to a mutated enzyme, MacTel patients have increased deoxysphingolipids as a direct consequence of their reduced serine levels (Gantner 2019). Therefore, we hypothesize that a lower serine dose may be as effective as a high dose in MacTel patients since we do not have to overcome a mutant enzyme. We will therefore evaluate the effect of both low- and high-dose serine treatment in this study. Elevated levels of deoxysphingolipids have also been seen in patients with diabetes and dyslipidemia (Zuellig 2014). In dyslipidemic patients it has been shown that fenofibrate (160 mg/day) reduces circulating deoxysphinganine levels (Othman 2015). We hypothesize that both serine and fenofibrate will reduce deoxysphingolipids in MacTel patients. The combination of serine and fenofibrate on deoxysphingolipid levels has not been tested, and it may have an additive effect.

This study is a proof-of-concept study. If this hypothesis is found to be true, we aim to begin a larger, long-term study that will evaluate in greater detail how these interventions affect circulating deoxysphinganine levels, retinal neurotoxicity and MacTel progression over time.

There will be six treatment arms, including a control group. One arm will be treated with low-dose serine treatment (200 mg/kg/day), a second arm with high-dose serine treatment (400 mg/kg/day), a third with 160 mg/day of fenofibrate, a fourth with both 200 mg/kg/day of serine and 160 mg/day of fenofibrate, a fifth with both 400 mg/kg/day of serine and 160 mg/day of fenofibrate, and a sixth arm with no treatment. This final arm will serve as the control group to monitor the normal variance of serine and deoxysphingolipid levels over time in MacTel patients since this is unknown. Changes in serum deoxysphingolipid levels will be used as the primary outcome. Amino acid and ceramide levels will also be evaluated. The participants will be followed for 10 weeks with visits at Screening, Week 0, 3, 6, and 10.

The randomization model will stratify patients by diabetes status, ensuring equal treatment of diabetics / non-diabetics in the study. Diabetes is a consideration in the randomization process because it is a metabolic disorder and can affect levels of circulating lipids, amino acids, and ceramide levels.

We will also collect gut microbiome (fecal) samples from participants to investigate the relationship between the patient microbiome and circulating amino acid and lipid levels. There are more microorganisms in the gut than cells in the human body. The abundance, diversity and activity of this gut microbiome can significantly impact an individual's health and has been associated with numerous diseases, including inflammatory bowel syndrome, diabetes, and cardiovascular disease. The gut microbiome is important for nutrient metabolism, both utilizing nutrients taken in from the diet and secreting nutrients for the host gut to absorb. MacTel patients have reduced blood levels of the amino acids serine and glycine, and we are testing to determine if these levels can be increased as a consequence of oral serine supplementation. It is unknown if the gut microbiome in MacTel patients is contributing to or altered due to the low systemic serine levels. Furthermore, it is unknown if and how the gut microbiome will be altered in response to oral serine supplementation. These samples will be analyzed by shotgun metagenomics to determine the distinct composition of the gut flora. By collecting these microbiome samples in parallel with serum samples from MacTel patients before, during, and after serine supplementation we hope to learn if the gut microbiome is altered due to serine supplementation and if this impacts the blood amino acid levels of the patients.

7. STUDY METHODS

7.1 Design:

- Prospective Clinical Trial
- Multi-site Phase 2a Study
- Open label (unmasked)
- One arm will be a control group
- 10-week follow-up
- Total patient recruitment: 60-120 participants
- Number of arms: 6

This is a prospective, controlled study of serum deoxysphingolipid in patients with MacTel.

Participants will undergo a screening evaluation to determine eligibility. Qualified participants must

meet all eligibility criteria and none of the exclusion criteria. At each visit a fasting blood sample will be collected. At the Baseline visit (Week 0), patients will be randomized. In randomization, participants will be stratified by diabetes status, ensuring equal treatment of diabetics / non-diabetics in the study. Participants will then begin dosing with either serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day and fenofibrate 160 mg/day, serine 400 mg/kg/day and fenofibrate 160 mg/day, or no treatment (control group) for 6 weeks, followed by washout of 4 weeks. Following the washout period, they will return for a final follow-up visit.

All participants will be followed for 10 weeks and blood will be collected at scheduled visits to measure serum deoxysphingolipid and metabolite levels during the course of treatment (Appendix I).

Participants will also collect a total of nine gut microbiome samples throughout study participation. These samples will be collected at home using provided kits in the week following the Screening (-1 visit), during Week 5, and during Week 9. Participants will collect three samples in each of these weeklong windows, store them at home per the instructions provided for a maximum of one week, and submit the samples to the clinical site at the in-person visit that follows each collection week. Detailed instructions regarding the sample collection and storage will be provided at the Week -1 visit.

7.2 Study Objective:

To evaluate changes in serum deoxysphingolipid levels in patients with MacTel type 2 following treatment with serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day and fenofibrate 160 mg/day, serine 400 mg/kg/day and fenofibrate 160 mg/day, or no treatment (control group).

7.3 Study Population:

Participants will be recruited from affected participants enrolled in the Natural History Observation and Registry (NHOR) Study of macular telangiectasia type 2.

7.4 Inclusion Criteria

To participate in this study, the potential participant **must meet** all of the following criteria:

1. Signed and dated written informed consent obtained from the participant in accordance with the local regulations;
2. Males/females 21 years of age or older;
3. English speaking;

4. Enrolled in the Natural History Observation and Registry Study (NHOR) and diagnosed with confirmed MacTel type 2 in at least one eye;
5. Willing to use contraception, if applicable; and
6. Willing to comply with study protocol and follow-up visits.

7.5 Exclusion Criteria

1. Participant is unable to provide informed consent;
2. Participant is less than 21 years of age;
3. Participant is currently taking, or has taken within four weeks prior to screening, a serine or glycine supplement;
4. Participant is currently taking, or has taken within 12 months prior to screening, fibrates including clofibrate, ciprofibrate, bezafibrate, fenofibrate, and gemfibrozil;
5. Participant is currently taking an anticoagulant, colchicine, cyclosporine, tacrolimus or bile acid binding resins;
6. Participant has known allergy to fibrates and/or serine;
7. Participant has a known history of clinically significant myopathy or myalgia related to cholesterol-lowering drugs;
8. Participant has active liver disease and/or elevated liver enzymes*;
9. Participant has renal dysfunction as evidenced by elevated serum creatinine* and/ or glomerular filtration rate (GFR) less than 60 mL/min;
10. Participant has thrombocytopenia as evidenced by a platelet count below 100,000 per microliter, anemia as evidenced by hemoglobin levels below 10 g/dL, or history of bleeding disorder;
11. Participant has a history of gallbladder disease or has had a cholecystectomy;
12. Participant has triglyceride levels greater than 400 mg/dL on treatment, or greater than 700 mg/dL on no treatment;
13. Participant has untreated/uncured Hepatitis C, or a history of Hepatitis B, autoimmune hepatitis, or HIV;
14. Participant has had any malignancies within the last 5 years (not including basal cell carcinoma);
15. Participant has ever been enrolled in a clinical trial involving ciliary neurotrophic factor (CNTF) treatment;
16. Participant is currently enrolled in another clinical trial involving treatment or participated in one within the last 30 days;

17. Participant is pregnant, breastfeeding or planning a pregnancy;
18. Participant is medically unable to comply with study procedures or follow-up visits;
19. Participant has, in the opinion of the Investigator, any physical or mental condition that would increase the patient's risk of participation in the study or may interfere with the study procedures, evaluations and outcome assessments; or
20. Patient is unavailable for follow-up visits.

**based on reference range for the local laboratory used*

7.6 Participant Recruitment

Participants will be recruited from participants enrolled in the MacTel NHOR Registry at selected registry sites. The study will enroll 60-120 participants.

Enrolled participants are those that have undergone screening, signed consent, and begun treatment.

If a person affected by MacTel type 2 is interested in participating, the investigator will confirm that the patient has satisfied the eligibility criteria and does not meet any of the exclusion criteria stated in the Study Protocol and the study will be discussed in full with the patient. The potential participant will be given a copy of the approved informed consent document for further consideration. The patient will have sufficient time to decide whether or not to take part in the study. All study procedures, including the nature of the study, the risks and benefits of the study procedures, and any possible adverse events will be described to the patient by the investigator or designee. The participant will be informed that he or she is free to *voluntarily* terminate participation in the study for any reason.

Any patient unwilling to participate at this stage will be managed through standard of care.

After agreeing to participate and signing the ICF, the study participant will undergo the Examination Procedures at the Screening (Week -1) visit. The data from these tests will be used for study data analysis.

8. STUDY PROCEDURES/VISITS

8.1 Screening (Week -1) Visit - initial assessment

- Informed Consent obtained
- Medical History: Full patient history including age, year of birth, gender, ethnic group, relevant and significant medical history, complete ocular history and concomitant medications at baseline
- BMI assessment (height and weight)
- Fasting blood for metabolite analysis, genetics if not already obtained through NHOR, serum chemistries to include *fasting glucose, sodium, potassium, albumin, bilirubin, BUN (urea), creatinine, chloride, bicarbonate (CO₂), alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), gamma glutamine transferase (GGT), and calculated GFR*, lipid panel (*including: total cholesterol, triglycerides, HDL, LDL, and VLDL*), lipase, creatine phosphokinase, complete blood count with differential (*including: red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit, mean corpuscular value (MCV), neutrophils, lymphocytes, monocytes, eosinophils, and basophils*) and HbA1c.
- Pregnancy test, if female of child-bearing potential
- Review of gut microbiome sample procedures and provision of sample kits. Participant will collect three samples in the week following Screening (Week -1) and return them to the clinical site at the Baseline (Week 0) visit.

8.2 Baseline (Week 0) Visit (+/- 3 days)

- Review of Inclusion/Exclusion Criteria (including screening laboratory results)
- Fasting blood for metabolite analysis
- Return of gut microbiome samples collected during the previous week.
- Ophthalmic Imaging (OCT and Small Pupil Fundus Photo)
- Randomization and receipt of assigned investigational product
- Review investigational product instructions with study coordinator
- Begin assigned investigational product regimen (Either serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day AND fenofibrate 160 mg/day, serine 400 mg/kg/day AND fenofibrate 160 mg/day, or no treatment)

8.3 Week 3 Visit (+/- 3 days)

- Adverse events assessment
- Concomitant Medications review
- Fasting blood for metabolite analysis, serum chemistries to include *fasting glucose, sodium, potassium, albumin, bilirubin, BUN (urea), creatinine, chloride, bicarbonate (CO₂), alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), gamma glutamine transferase (GGT), and calculated GFR*, lipid panel (*including: total cholesterol, triglycerides, HDL, LDL, and VLDL*), lipase, creatine phosphokinase, complete blood count with differential (*including: red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit, mean corpuscular value (MCV), neutrophils, lymphocytes, monocytes, eosinophils, basophils*).
- Treatment compliance
- Pregnancy test if female of child-bearing potential
- Review of gut microbiome sample procedures and provision of sample kits. Participant will collect three samples during Week 5 and return them to the clinical site at Week 6.

8.4 Week 6 (+/- 3 days)

- Adverse events assessment
- Concomitant Medications review
- Fasting blood for metabolite analysis, serum chemistries to include *fasting glucose, sodium, potassium, albumin, bilirubin, BUN (urea), creatinine, chloride, bicarbonate (CO₂), alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), gamma glutamine transferase (GGT), and calculated GFR*, lipid panel (*including: total cholesterol, triglycerides, HDL, LDL, and VLDL*), lipase, creatine phosphokinase, complete blood count with differential (*including: red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit, mean corpuscular value (MCV), neutrophils, lymphocytes, monocytes, eosinophils, basophils*).
- Return of gut microbiome samples collected during Week 5.
- End of assigned investigational product regimen/Begin washout period
- Treatment compliance
- Review of gut microbiome sample procedures and provision of sample kits. Participant will collect three samples during Week 9 and return them to the clinical site at Week 10.

8.5 Week 10 (+/- 3 days)

- Adverse events assessment
- Concomitant Medications review
- Fasting blood for metabolite analysis, serum chemistries to include *fasting glucose, sodium, potassium, albumin, bilirubin, BUN (urea), creatinine, chloride, bicarbonate (CO₂), alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), gamma glutamine transferase (GGT), and calculated GFR*, lipid panel (*including: total cholesterol, triglycerides, HDL, LDL, and VLDL*), lipase, creatine phosphokinase, complete blood count with differential (*including: red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit, mean corpuscular value (MCV), neutrophils, lymphocytes, monocytes, eosinophils, basophils*).
- Return of gut microbiome samples collected during Week 9.
- Exit study

9. STUDY PROCEDURES/DEFINITIONS**Fasting blood samples:**

- At every visit: 5 ml blood sample will be collected to obtain serum for metabolite analyses.
- Week -1: blood will be collected for HbA1c levels.
- Weeks -1, 3, 6 & 10: blood samples will be collected for serum chemistries to include *fasting glucose, sodium, potassium, albumin, bilirubin, BUN (urea), creatinine, chloride, bicarbonate (CO₂), alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), gamma glutamine transferase (GGT), and calculated GFR*, lipid panel (*including: total cholesterol, triglycerides, HDL, LDL, and VLDL*), lipase, creatine phosphokinase, and CBC with differential (*including: red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit, mean corpuscular value (MCV), neutrophils, lymphocytes, monocytes, eosinophils, and basophils*).
- Week -1: If not already obtained through NHOR, 10 ml whole blood will be collected for genetic testing, assuming participant consents.

BMI: Body mass index (BMI) is a measure of body fat based on height and weight.

Gut Microbiome samples: The participant will collect and submit a total of 9 gut microbiome samples for microbiome activity testing. Three samples will be collected

before the baseline visit (Week 0), three during Week 5, and three during Week 9. Detailed instructions on sample collection and submission will be provided to all participants at the Screening visit and reviewed at Weeks 3 and 6.

Treatment: Participants will be assigned to one of the following treatment groups: serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day AND fenofibrate 160 mg/day, serine 400 mg/kg/day AND fenofibrate 160 mg/day, or no treatment (control group).

Optical Coherence Tomography (OCT): An OCT test uses a very thin light beam to create an image of the retina. This test also measures retinal thickness and takes only a few minutes.

Fundus Photography: A small-pupil (undilated) image will be obtained of the retina.

10. PARTICIPANT WITHDRAWAL

All participants have the right to withdraw from the study with or without a stated reason, and without prejudice to future medical care or legal rights. When a participant withdraws from the study voluntarily, a reasonable effort should be made to determine the reason for premature withdrawal in order to determine whether an adverse event caused the termination. In addition, a reasonable effort should be made to have participants who receive treatment return to complete tests and evaluations listed for the Week 10 visit prior to discontinuing the study.

The PI or Sponsor may discontinue a participant from the study at any time due to safety concerns or the inability to comply with study requirements. The Sponsor also retains the right to end the study at any time for any reason.

Participants who withdraw from the study before the Week 10 visit may be replaced to ensure sufficient data is available for analysis.

11. CONCOMITANT MEDICATIONS AND CONCURRENT PROCEDURES

Any concomitant medications a participant is receiving at the start of the study or given for any reason during the study must be recorded in the source document, including start and stop dates and indication information. Recording of concomitant medications will be done on the Case Report Forms (CRFs).

In addition, all ocular and non-ocular procedures that take place during the study must also be recorded in the Concurrent Procedures log.

Participants prescribed fibrates or taking serine or glycine supplements will not be allowed to participate. Due to drug interactions with fenofibrate, other prohibited medications include anticoagulants, colchicine, cyclosporine, tacrolimus and bile acid binding resins.

12. MASKING

This is an open-label study. Participants will be told if they are taking serine and/or fenofibrate, or if they are participating as a control (no treatment).

13. STUDY RISKS/ RISK REDUCTION

Blood Sample Risk: Drawing blood can cause pain, bruising, or infection where the needle is inserted. Some people experience dizziness, fainting, or upset stomach when their blood is drawn. Only trained and qualified personnel will perform blood draws, following standard blood draw procedures.

Fasting Risks: Fasting could lead to headaches, dizziness and faintness. Participants will be reminded of these risks and encouraged to schedule visits earlier in the day to mitigate these issues.

Serine 200 mg/kg/day and 400 mg/kg day: A Phase I safety trial reported that some patients taking 5-15 g of serine twice daily reported bloating and nausea (Levine 2016). The FDA classifies L-serine as a GRAS (generally regarded as safe) food supplement, providing that it is below 8.4% of total protein in an individual's diet (FDA CFR Title 21 Section 17.320.18). The doses of Serine used in this study have been used in prior studies and for longer periods of time without safety issues being reported (Garofalo 2011).

Fenofibrate 160 mg/day: Fenofibrate is an FDA-approved medication indicated for lowering serum lipid levels and has been in widespread use for many years with a particularly good safety profile. Standard dosing will be used in this study.

Fenofibrate is an FDA-approved drug. The FDA label warning states that myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. This risk is increased when

fenofibrate is co-administered with statins, particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism.

Strict eligibility criteria were designed to prevent enrollment of persons who may be at risk for known side effects. The design of the protocol, especially the compiling of the Inclusion and Exclusion criteria and potential risks, was based on the ACCORD Study (Action to Control Cardiovascular Risk in Diabetes). The ACCORD study was a long-term study employing fenofibrate as a treatment or prevention for diabetic retinopathy. The study included one arm in which fenofibrate and statins were used together. There was no increase in risk seen in this group. (Myositis – 0.04%; 0.06% (standard glycemic control; intensive glycemic control) Rhabdomyolysis - 0.02%; 0.04% (standard glycemic control; intensive glycemic control. Laboratory results, including fasting glucose, sodium, potassium, albumin, bilirubin, BUN (urea), creatinine, chloride, bicarbonate (CO₂), alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), gamma glutamine transferase (GGT), and calculated GFR, lipid panel (including: total cholesterol, triglycerides, HDL, LDL, and VLDL), lipase, creatine phosphokinase, complete blood count with differential (including: red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit, mean corpuscular value (MCV), neutrophils, lymphocytes, monocytes, eosinophils, and basophils) will be measured before, during and after study participation to monitor safety.

Laboratory results will be reviewed in a timely manner by the site principal investigator or sub-investigator (sub-I) and the sponsor's clinical team. In the event that any of these laboratory values increase or decrease outside of the normal range or baseline values, a discussion will take place between the sponsor's clinical team and the PI or sub-Investigator to determine if a change in the course of action should take place. This could be a repeat laboratory test, changes in investigational product or termination from IP administration. Clinically significant changes may, however, require immediate action of the site's principal investigator or sub-I and need to be reported to the sponsor in a timely manner.

Any abnormal values will be followed until acceptable resolution by the sponsor and PI. For example, outcome may include a return to normal or baseline values, determination that abnormality is not related to IP or determination that abnormal value is not clinically significant.

OCT: Optical Coherence Tomography is an FDA-approved imaging technique, which is not associated with any adverse events.

Fundus Photo: Fundus photography is not associated with any adverse events, although some participants may experience some discomfort due to the bright lights.

Loss of confidentiality: Loss of confidentiality is always a risk but all reasonable measures will be taken to maintain participant privacy. Participants will be provided a unique study identifier that will be used in all correspondence with the sponsor. The site will maintain study records in a secure location. No identifying information will be used in any publications or presentations that result from this study.

Every effort will be made to ensure the confidentiality of the participants' private information, but it is not an absolute guarantee. Data sent to the sponsor will be coded and referred to by Subject ID only. No identifying information will be used in reports, presentations or publications.

The participants' year of birth will be submitted to the sponsor. The local laboratory processing the blood work may require the full date of birth and the results may be placed in the participants' medical record at the site. Participants will be made aware of this during the consenting process.

13.1 Safety Monitoring

This study will not be monitored on site by the sponsor. Study compliance will be monitored via the electronic data entry system and queries generated as issues are identified. The sponsor will monitor any adverse event reporting.

Due to the short time of study participation (11 weeks) and short time of administration of investigational products (6 weeks), a Data Safety Monitoring Board will not be used for this study. Per GCP Guidelines, the sites are expected to enter visit data within 24 hours of the visit. Laboratory results are to be reviewed and signed by the PI or sub-I within 24 hours of receipt and the redacted results uploaded to the data entry system. Adverse Events should be entered as the site becomes aware, especially if between visits. Serious Adverse Events are to be relayed to the relevant IRB and the sponsor within 24 hours.

Any change in clinical status, laboratory values, or symptoms reported by a participant is considered an AE. The PI or sub-I will determine severity, clinical significance and causality to IP/study procedures. If changes pose a risk to a participant's safety and require immediate action, the PI or sub-I will determine adequate measures.

Data will be monitored by the sponsor in "real time", meaning within 24-48 hours of the data being entered. Any entry denoting a possible safety issue will be reviewed and addressed by the sponsor's clinical team. Site notification will be relayed to the PI or sub-I

and Study Coordinator and a discussion will take place to determine a course of action, if necessary. This could be a repeat laboratory test, changes in investigational product or termination from the IP administration portion of the study.

13.2 Risk/Benefit

There may be no benefit to the participants enrolled in this Phase 2a Study. However, results from this Phase 2a study may lead to a larger and longer study to evaluate the effect of serine and/or fenofibrate treatment on ocular changes in MacTel patients.

Incidental findings will be managed by the investigator at the clinical site. Adverse events determined to be study related will be followed until satisfactory resolution.

13.3 Alternative Therapies

There is currently no known treatment for macular telangiectasia type 2. This is not a treatment study for MacTel.

14. ADVERSE EVENT REPORTING

All adverse events (AEs) either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously or in response to direct questioning, will be reported. Any adverse event, regardless of severity or potential association with the study treatments or study procedures, must be documented in study records and appropriately reported.

AEs will be reported within the participant's records and reported to the sponsor within a timely manner by the site personnel. All AEs will be recorded from the date of obtaining informed consent until the last study visit.

The sponsor's clinical team will evaluate all reported adverse events on an ongoing basis.

Serious adverse events (SAEs) will be followed until resolution or until stability is reached. In rare instances, this may include following the participant after completion of the study.

All serious adverse events should be reported to the Sponsor within 24 hours of identification. The SAE will be reported to the Sponsor via a 24-hour monitored email address provided to the clinical site. All SAEs should be reported to local Institutional Review Boards/Ethic Committees (IRBs/IECs) per local IRB/IEC requirements.

15. DEFINITIONS

15.1 Adverse Events

An adverse event is any untoward medical occurrence in humans, whether or not considered treatment- or procedure-related, which occurs during the conduct of a clinical trial. Any change in clinical status, laboratory values, or symptoms is considered an AE. Medical conditions or diseases present at the screening visit should be recorded as medical history and are only considered adverse events if they worsen after the screening visit (temporal association).

15.2 Suspected adverse reaction (Related Adverse Event) is any adverse event for which there is a reasonable possibility that the treatment and/or study procedures caused the adverse event. A reasonable possibility implies that there is evidence that the treatment and/or study procedures caused the event.

15.3 Serious Adverse Events

A serious adverse event (SAE) as determined by the Investigator or the Sponsor is any event that results in any of the following outcomes:

1. Death;
2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the Investigator or Sponsor, at immediate risk of death from the event as it occurred.);
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
4. Inpatient hospitalization or prolongation of existing hospitalization;
5. Congenital abnormality or birth defect; or
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Note that the term “serious” is not a measure of severity but speaks to a very specific definition as noted in 1-6 above.

A hospitalization for an elective or cosmetic procedure, scheduled prior to enrollment or during the course of the study, unrelated to the medical condition under study, is excluded from this definition of a serious adverse event.

15.4 Unexpected Adverse Event

An unexpected adverse event is an event where the specificity or severity of which is not consistent with the current approved product labeling for the test article.

This includes an increase in the frequency or severity of a previously reported adverse event that is significantly above the rates known from previous experience with the test article.

15.5 Guidelines for Determining when Changes in Pre-Existing Conditions are Considered Adverse Events

Adverse events include illnesses with onset during the study or exacerbations of pre-existing illnesses. Exacerbation of pre-existing illness is defined as a clinically relevant increase in the severity of the illness as compared to the start of the study and should be considered when a participant requires new or additional treatment for that illness. Investigators should use the following guidelines to assess when an adverse event needs to be reported for a condition which results in a change to an ongoing medication and/or addition of a new medication:

- Addition of a new medication and/or change in ongoing medication due to an untoward (unfavorable and unintended) change in a participant's medical health for a disease/condition documented as ongoing at baseline.
- Addition of a new medication due to an untoward (unfavorable and unintended) change in a participant's medical health for a disease/condition not present at baseline.

15.6 Guidelines for Assessing Intensity of an Adverse Event

The Investigator should use the following definitions when assessing Intensity of an Adverse Event:

- MILD: Transient (< 48 hours) or mild discomforts, no or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities.
- MODERATE: Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required; hospitalization possible.
- SEVERE: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely.

- LIFE THREATENING: Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable.
- FATAL: Death

15.7 Guidelines for Determining Causality of an Adverse Event

The Investigator will answer the following question when assessing causality of an adverse event to study treatment/ procedures: “Is there a reasonable possibility that the study treatment and/or procedures caused the event?” A reasonable possibility implies there is evidence that the specific event was caused by the study treatment and/or procedures. An affirmative answer designates the event as a suspected adverse reaction, and the AE is therefore considered “related.” If the answer is no, then the AE is considered “unrelated.”

15.8 Obligations of Investigators

The Investigator is obligated to promptly report all adverse events. When submitting adverse event information, the Investigator may not delegate to someone other than a listed study physician the responsibility for reviewing the accuracy of the contents of an adverse event report. When reporting an adverse event, the Investigator must assign a severity grade to each event and also declare an opinion on the causality of the event relative to the study test article or procedure.

For any serious adverse event, the IRB and Sponsor must be notified **within 24 hours** of when the Investigator first learns of the occurrence of the event.

If the participant reaches the final scheduled follow-up visit, any new adverse events, as well as follow-up information for ongoing adverse events, must be recorded. For participants who withdraw prematurely, adverse events should be followed until 30 days after last study visit. In any case, every attempt must be made by the Investigator to follow serious adverse events that are not resolved or medically stable within 30 days of the last study visit until they become resolved or medically stable.

15.9 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an adverse event. It is unknown if the study medication/supplement can affect an unborn child. A confirmed pregnancy in a study participant should be reported to the sponsor as soon as the fact has been reported.

Any pregnancy diagnosed during the study must be reported immediately to the Investigator. The Investigator will notify the Sponsor. Any participant that becomes pregnant during the treatment period will no longer receive their assigned treatment. However, the participant should continue follow-up visits to assess for safety. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be documented on a form that will be provided by the Sponsor. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Sponsor. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, should not be considered as adverse events.

15.10 Notifying the Sponsor

The Investigators will provide the Sponsor with data of all SAEs as defined per the protocol on an ongoing basis. As noted above, this should be within 24 hours of site awareness of the event. The Medical Monitor will review each SAE report.

15.11 Early Termination or Participant Discontinuation

Participants may choose to withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other clinical protocols.

The Investigator may discontinue a participant from the study if warranted. The Investigator and the Sponsor may also request the withdrawal of a participant because of non-compliance (e.g., missed visits), administrative reasons or any other valid and ethical reasons.

Reasons for participant discontinuation may include, but are not limited to, the following:

- Investigator determination that it is not in the best interest of the participant to continue participation
- Intercurrent illness
- Adverse event
- Worsening condition
- Any other safety concerns

If a participant withdraws or is discontinued from the study, they should return for an exit visit. The schedule of assessments for this visit is the same as that for the final visit.

The Sponsor may terminate the study earlier than planned for any reason. In the event of early termination, the Sponsor will notify the Investigators and IRBs of the decision and will provide all relevant information.

16. STATISTICAL CONSIDERATIONS

Overview of Study Design

16.1 Sample Size Estimates

The study will enroll 60-120 eligible participants (10-20 participants per treatment group).

16.2 Randomization

A permuted block design will be used to randomize participants in a 1:1:1:1:1:1 ratio to either 1) serine 200 mg/kg/day, 2) serine 400 mg/kg/day, 3) fenofibrate 160 mg/day, 4) serine 200 mg/kg/day AND fenofibrate 160 mg/day, 5) serine 400 mg/kg/day AND fenofibrate 160 mg/day, or 6) no treatment (control group). This scheme is to ensure equal numbers of participants in each arm.

16.3 Statistical Analysis

Due to the exploratory nature of the study and the small number of participants per treatment group enrolled in this study, the data will be analyzed by descriptive statistics. Summary statistics will be presented by randomized treatment group.

In general, no replacement of missing data or removal of data will be conducted.

16.4 Primary Endpoints

The primary endpoints will be serum deoxysphingolipid levels, as well as other lipid and amino acid levels.

The primary time points for the primary safety outcomes will be reviewed at 3, 6 and 10 weeks, unless otherwise stated.

16.5 Safety Outcomes

Safety assessment of the treatment will include (AEs) and serious adverse events (SAEs) as noted in the examinations at study visits and self-reported by the participants during and between study visits.

Adverse events of interest for this study include the following:

- Symptoms including; muscle pain, tenderness or weakness, abdominal pain, easy bruising or bleeding
- Changes in blood measures including; creatinine, eGFR, ALT, AST, CPK, HDL, and lipase
- Diseases including; Myopathy, Rhabdomyolysis, Pancreatitis, Cholelithiasis, Rhinitis, Pulmonary embolus (PE) and deep vein thrombosis (DVT), Anemia, Agranulocytosis, and Thrombocytopenia

16.6 Adverse Events

The number and percentage of participants with treatment emergent/incident adverse events (e.g., started or increased in severity after the participant received study treatment) will be summarized. Related AEs will be summarized. No formal statistical analyses will be employed.

17. DATA QUALITY ASSURANCE

The sponsor will have the primary responsibility for assuring that the quality of the data collected and reported in the study are of consistently high quality. Many factors contribute to the quality of the data, from the design and procedures of the trial to the analytic methods employed.

The major quality assurance features of the study are:

Standard data collection forms and procedures;

Common protocol for eligibility, examination and follow-up of all participants in all clinical centers;

- Standardized medications; and
- Frequency of study visits to report and assess AEs and SAEs.

18. HUMAN PARTICIPANT PROTECTION – INFORMED CONSENT

All participants will receive a verbal explanation from the Principal Investigator or his/her appropriate designee in terms suited to their comprehension of the purposes, procedures and potential risks of the study. In the opinion of the Principal Investigator or designee, the participants must be capable of comprehending the contents of the informed consent and able to sign an informed consent form, which must be obtained prior to enrollment. The participants will have an

opportunity to review the consent form carefully 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.

The participants' names will not appear on any of the data forms reported to the Sponsor. Participants will be identified by a study number. The participants' year of birth will be collected in the data system as a second identifier. The information collected will remain confidential.

19. INVESTIGATOR REQUIREMENTS

This study will be conducted in accordance with Good Clinical Practice (GCP), using the guidance documents and practices offered by ICH and FDA, and in accordance with the Declaration of Helsinki. This study will also comply with the regulations 21 CFR Parts 50, 56.

19.1 Institutional Review Board / Institutional Ethics Committee Review

This Phase 2a study will not require prior approval from the FDA, as both investigational products are cleared for general consumption and the investigators are not seeking a new indication. Approval must be obtained by the relevant IRB of the local institution. The IRB will conform to the standards of ICH E6 and the Code of Federal Regulations, specifically 21 CFR Part 56. The IRB will be provided with copies of the protocol, amendments, participant information and consent forms for review. Independent ethics committee approval must always be recorded in writing. The approval documents should clearly identify the protocol by title and an IRB identifying number.

The IRB will conduct continuing reviews for the study at appropriate intervals. The IRB must keep records of all its procedures and decisions for at least three years after completion of the trial and make them available on request to representatives of regulatory authorities, if applicable.

19.2 Study Monitoring Requirements

This study will not be monitored on site by the sponsor. Study compliance will be monitored via the electronic data entry system and queries generated as issues are identified. The sponsor will monitor any adverse event reporting.

The sponsor reserves the right to visit the site and inspect the records at any time. To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or their representative may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an audit or inspection, the Principal Investigator (and institution) must agree to grant the monitor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues. The Principal Investigator will permit the Sponsor representatives, other regulatory agencies, Institutional Review Boards and the respective national or local health authorities to inspect facilities and records relevant to this study.

19.3 Case Report Forms and Data Collection

Data must be transcribed from the patient's notes and/or source documents and entered onto the Case Report Form (CRF) provided by the sponsor, completely, legibly and in a timely fashion by the PI or his designees. The PI will verify that all data contained on these forms are accurate and will sign the forms once they are completed. The completed forms will be transmitted to the sponsor.

Any alterations to data must be made by striking out the previous entry with a single line and by writing the new value next to it. The changes must also be captured within the CRF. All changes must be initialed and dated by the PI (or his designee). Writing or scribbling out of errors is not acceptable.

The PI will retain all study related documents in a secure but accessible place.

19.4 Disclosure of Data

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the participant, or unless permitted or required by law.

Medical information may be given to a participant's physician or other appropriate medical personnel responsible for the participant's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of regulatory agencies, national and local health authorities, Sponsor representatives and the IRB/IEC for each study site, if appropriate.

20. STUDY TERMINATION

The study may be terminated at any time by the Principal Investigator or the Sponsor with appropriate notification.

Participants currently enrolled in the study will be notified and exited. Study related AEs may be followed until there is satisfactory resolution.

21. RETENTION OF RECORDS

No records should be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor for transfer of any records to another party or moving them to another location.

22. REFERENCES

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(<https://clinicaltrials.gov/ct2/show/NCT00000620?term=ACCORD&draw=2&rank=1>)
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APPENDIX I

Assessment/Examination Schedule

	Week -1 Visit 1	<i>before week 0</i>	Week 0 (+/-3 days) Visit 2	Week 3 (+/-3 days) Visit 3	<i>during week 5</i>	Week 6 (+/-3 days) Visit 4	<i>during week 9</i>	Week 10 (+/-3 days) Visit 5
GENERAL ASSESSMENTS	Screening		Begin treatment			Stop treatment		
Informed Study Consent	X							
Review Eligibility Criteria	X		X					
Demographics and Participant Contact Information	X							
Medical & Ophthalmic History	X							
AE Assessment – <i>starting from Week 0</i>			X	X		X		X
Concomitant Medications	X		X	X		X		X
Height and Weight for BMI Assessment	X							
Pregnancy Test ¹	X							
Ophthalmic Imaging: OCT			X					
Ophthalmic Imaging: Fundus Photo			X					
Gut Microbiome (Fecal) Sample Collection and Submission (x3 within each window of time) ²		X			X		X	
Fasting Blood Sample for de-oxy	X		X	X		X		X
Blood Sample - Chemistry/Lipid panel/Lipase/Creatine phosphokinase/CBC with differential/HbA1c ³	X			X		X		X
Blood sample for Genetics ⁴	X							
Randomization & Begin Treatment (serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day AND fenofibrate 160 mg/day, serine 400 mg/kg/day AND fenofibrate 160 mg/day, or no treatment (control group))			X					
Stop Treatment						X		
Medication Compliance				X		X		

1. For women of childbearing potential

2. Participant collects at-home; if participant has strong aversion to microbiome sample collection, but otherwise meets eligibility criteria, they can still participate in the study

3. HbA1c only performed at the screening visit

4. If not previously collected at NHOR enrollment and participant cons