MET*FOR*MIN CLINICAL TRIAL:

METformin administration FOR the MINimization of geographic atrophy progression in patients with dry Age-Related Macular Degeneration (NCT02684578)

PROTOCOL

Version 1.20
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CHAPTER 1: Background & Summary

1.1 Background:

1.1.1 Why is this study important?

Age-related macular degeneration is currently the leading cause of severe vision loss in people over the age of 50. In the United States, AMD affects at least 11 million individuals and 1.2 million individuals are legally blind as a result (1). AMD is classified into two types: "wet" AMD, characterized by choroidal neovascularization, and "dry" AMD, characterized by the presence of drusen under the macula and eventually in later stages, by geographic atrophy of retinal pigment epithelial (RPE) cells associated with subsequent loss of overlying photoreceptors. While there are currently a few treatment options shown to decrease the progression of the wet form of AMD, there are no proven medical treatments to reverse or slow the progression of dry AMD. While wet AMD generally results in much more rapid loss of central vision, only about 10% of AMD cases take this form, and dry AMD always precedes the neovascular form. The number of people in the US with AMD is estimated to double by the year 2050, as the population ages (2). This condition is not only devastating to patients facing blindness, but it is also a major economic burden with the global cost of visual impairment due to AMD estimated to be $343 billion (3).

1.1.2 Clinical Observations and Current Standard of Care for Patients with GA

Geographic atrophy in patients with AMD has discrete characteristics and is thus diagnosed readily. In areas of atrophy, decreased retinal thickness is apparent on optical coherence tomography. GA also appears in fundus photography, as the areas of thinning retina appear lighter that the surrounding unaffected retina, and choroidal vessels may be more easily visualized in these thin atrophic areas. Moreover, fundus autofluorescence can be a valuable tool used to confirm the diagnosis of GA and track GA progression, as atrophic areas appear hypofluorescent (4).

In terms of patient experience, GA generally initially arises in the area surrounding the fovea, sparing central vision (5). This manifests itself in the form of impaired vision in dim light, dark adaptation difficulty, less contrast sensitivity, and worsening near vision usually apparent during reading. As the disease process evolves with enlargement of GA, the fovea may not be spared in the later stages, and atrophy at this point leads to loss of central vision (4).

The current standard of care for patients with GA simply involves observation and close monitoring by retina specialists, as there is no proven intervention to stop or slow the progression of GA. Follow-up of these patients ensures that should patients develop neovascularization, the correct course of action is taken, since this form of AMD can be treated via intravitreal anti-VEGF treatments, photodynamic therapy, or photocoagulation (6). Actual management of dry AMD is limited to modification in lifestyle including diet and exercise regimens, cessation of smoking, vitamin supplements and low-vision rehabilitation in the later stages (7).

1.1.3 Pathophysiology of Geographic Atrophy in AMD

Though the pathophysiology of GA in AMD is still not fully understood, a growing body of evidence exists to support the role of chronic inflammation potentially caused by metabolic product accumulation in the extracellular space between the RPE cells and Bruch's membrane (7). Thus, it is hypothesized that the activation of the complement system via increase in oxidative stress may play a significant role in the etiology of this disease.

This theory is supported by several findings, including the discovery of complement system proteins within the drusen of patients with AMD. Moreover, genes involved in the complement activation cascade, including CFH, CFHR1, CFHR3, CFB, C2, and C3 have been implicated in AMD pathogenesis in several genetic studies. Most sequence variants of these complement-pathway associated genes result in increased susceptibility to AMD development, as unlike the unchanged genes, these gene variants fail to inhibit the complement pathway. On the other hand, CFHR1 and CFHR3 variants were found to be protective. Despite sequence similarity to CFR, these genes appear to act downstream of C3, the target of CFH's inhibition (8). Further genetic support for this pathophysiology is provided by a study showing that in populations of European descent, polymorphisms in the Complement factor H locus and the Complement factor B/Complement component 2 locus may be responsible for up to 75% of AMD cases (9).

1.1.4 Metformin Overview

Metformin is a potent antihyperglycemic drug that is recommended by the American Diabetes Association as the first line of oral defense in the treatment of type 2 diabetes (10). This drug, belonging to the biguanide class, was first described in scientific literature in 1921, and became available for human use in the United Kingdom in 1958 (11, 12). It received FDA approval in the United States in 1994.

The effect of metformin is primarily the acute decrease in hepatic glucose and secondary improvement of glucose uptake. Unlike most treatments for T2DM, metformin has a very low risk for hypoglycemia. It has relatively mild side-effects, with the most common being gastrointestinal distress. GI side effects are dose-dependent, and can usually be overcome via stepwise dose increases (13). The most serious side effect is lactic acidosis, and while this can be life-threatening it is uncommon, with Brown et al in 1998 reporting an observed rate of 9.7 cases in >41,000 person-years of experience (14). While the mechanisms of action by which metformin works to treat patients with T2DM are not fully understood, its inhibition of mitochondrial complex I and the resulting activation of AMPK is thought to play a major role in the decrease of hepatic glucose production (15).

1.2 Justification: Mechanisms of action by which metformin may decrease progression of Drusen accumulation and Geographic Atrophy in Patients with dry AMD

There are multiple potential mechanisms by which metformin could act to reduce the progression of drusen accumulation and geographic atrophy in patients with AMD. These include but are not limited to some of the following, many of which are intertwined or related. Due to metformin affecting several different pathways and processes, it likely utilizes varying mechanisms of action to produce beneficial phenotypes.

Reduction of Oxidative Stress

- There are multiple studies supporting the role of oxidative stress in AMD and its development (16)
- Several trials involving antioxidants, vitamins, and mineral supplements can potentially slow AMD progression (17, 18, 19), although long term (after 10 years) this effect of slowed progression was only seen in NV AMD, but not central GA
- Metformin is used to reduce oxidative stress, and specifically it has been shown to reduce the levels of oxidative stress markers in diabetics compared to baseline values and compared to control subjects who underwent lifestyle modifications without medication (20)

Reduction of Inflammation

- Drusen, deposits present beneath the retinal pigment epithelium in AMD, contain a variety of pro-inflammatory proteins, including fibrinogen, vitronectin, and complement components, as well as C-Reactive Protein (CRP).
- High levels of C reactive protein have been associated with a greater future risk of AMD (21), and higher levels are also associated with AMD progression (22, 23)
- CRP is a mediator of complement action→ Genentech is studying lampalizumab for AMD which affects complement pathway (Phase 3 Clinical Trial: https://www.clinicaltrials.gov/ct2/show/NCT02247479)
- Metformin has been shown to decrease CRP levels in women with PCOS (off label use of the drug), (24); it also decreased CRP in patients with T2D (25, 26)

mTOR Pathway

- The mTOR pathway is potentially activated in AMD. Evidence for this theory includes one study in which mitochondrial DNA were selectively ablated in mice RPE cells, resulting in RPE morphological changes similar to those seen in AMD. The most prominent early RPE changes were hypertrophy and dedifferentiation, which coincided with activation of the mTOR pathway in OXPHOS-deficient RPE cells (27)
- Metformin inhibits mTOR. One proposed mechanism of action: it accumulates in the mitochondria where it inhibits complex 1. This decreases ATP production and conversely increases AMP levels. High AMP levels activate AMPK, which then inhibits the mTOR signaling pathway. Alternatively, some think that metformin may activate AMPK directly at this point in the pathway (28)

Mitochondrial function

- In AMD, damaged mitochondria result in a deficit in RPE oxidative phosphorylation, eventually leading to photoreceptor degeneration and RPE morphological changes (27). Moreover, damaged mitochondrial DNA has been linked to AMD; thus mitochondria might be a good target for AMD treatment (29, 30)

- Metformin decreases mitochondrial respiration (31). Thus it is possible that metformin could decrease the oxidative stress that causes the damage to mtDNA in patients with AMD.

Potential for Weight Loss

- Obesity/Higher BMI is a risk factor for AMD (32)
- Metformin has been shown to reduce weight in non-diabetic obese patients (both insulin sensitive and insulin resistant) over a period of 6 months (33)
- Metformin has been shown to reduce weight in non-diabetic adult and children taking antipsychotic meds (34)
- Metformin's use for the sole purpose of weight reduction is still controversial based upon insufficient evidence supporting its efficacy (35)

1.3 Study Design Overview

Major Eligibility Criteria: See Chapter 2

- People aged 55 or older with AMD with soft drusen, at least one of which is greater than or equal to 63 microns in diameter, and/or with geographic atrophy in one or both eyes

Study Groups:

Subjects will be randomly assigned (1:1) to either:

- Metformin Treatment Group: this group will take Metformin daily throughout the duration of the 18 month interventional study period (see detailed dosage information in Chapter 3). In addition to taking this drug, this group will maintain the standard of care exam schedule for patients with dry AMD, including follow-up exams on a 6 month basis. This group will have an eGFR test at baseline and at one year to monitor kidney function.
- Observation Group: the subjects assigned to this group will follow standard of care protocol for dry AMD, which simply consists of monitoring the progression on a 6 month basis.

Sample Size: See details in Chapter 5

- 186 subjects from all study sites

Visit Schedule (timed from randomization)

- Enrollment exam/ 0 months
- 1 week phone call—to ensure that treatment group has picked up prescription and subjects have begun taking metformin
- 6 month follow-up exam
- 12 month follow-up exam
- 18 month follow-up
- 24 month follow-up/ Final exam

1.4 Study Aims

- To determine whether oral Metformin HCl is an effective treatment for slowing the

progression of drusen accumulation or geographic atrophy in patients with dry Age-related Macular Degeneration

CHAPTER 2: SUBJECT ENROLLMENT

2.1 Eligibility Assessment

2.1.1 Inclusion Criteria

- Subject must be >/= 55 years of age
- Subject must have evidence of dry AMD, defined by the characteristic presence of drusen and/or pigmentary changes with or without geographic atrophy. GA is defined as one or more well-defined and often circular patches of partial or complete depigmentation of the RPE, typically with exposure of underlying choroidal blood vessels. Even if much of the RPE appears to be preserved and large choroidal vessels are not visible, a round patch of RPE partial depigmentation may be classified as early GA. The GA in the study eye must be able to be photographed in its entirety, and it must not be contiguous with any areas of peripapillary atrophy, which can complicate area measurements.
- Subject must have clear ocular media and adequate pupillary dilation
- Subject must be able to swallow capsules
- Study eye must have best corrected visual acuity (BCVA) of 20/20-20/400
- Subject must be willing and able to pay for monthly prescription of Metformin HCl for 18 months in the event that their insurance carrier will not cover the cost of the drug

2.1.2 Exclusion Criteria

- Subjects with a baseline size of GA > 17.5mm^2 (7.0 Macular Photocoagulation Study Disc Areas).
- Subjects who are already taking metformin for another purpose
- Subjects with type 1 or 2 diabetes
- Subjects with compromised kidney function:
  -Serum creatinine ≥1.5 mg/dL for males and ≥1.4 mg/dL for females
  -eGFR levels below 45
- Subjects with moderate to severe heart failure (Class III or IV, New York Heart Association Functional Classifications)
- Subjects with Child's class C cirrhosis
- Subjects who are: pregnant women, adults who cannot consent for themselves, and those who use alcohol in excess
  - Excess alcohol use is defined by binge drinking (pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL) on 5 or more days in the past month
- Evidence of retinal atrophy due to causes other than atrophic AMD.
- Subjects who have had anti-VEGF injections or active choroidal neovascularization in the study eye during the last 12 months
- Current evidence or history of ocular disorders in the study eye that in the opinion of the investigator confounds study outcome measures, including (but not limited to):
  a. Non-proliferative diabetic retinopathy involving 10 or more hemorrhages or

microaneurysms, or active proliferative diabetic retinopathy
b. Branch or central retinal vein or artery occlusion
c. Macular hole
d. Pathologic myopia
e. Uveitis
f. Pseudovitelliform maculopathy
g. Intraoperative surgery within the last 90 days prior to study eye enrollment

2.2 Informed Consent

During a standard ophthalmic exam in clinic, a study investigator will determine if a patient meets the eligibility criteria for this study. S/he will then explain this study to the patient and if the patient would like to proceed with participation in this clinical trial, the investigator will obtain written consent at that visit. If the patient requires additional time to consider participation and discuss the study with others, this will be accommodated for, and the patient can be enrolled at his or her next exam.

2.3 Procedures at the Enrollment Visit

Prior to subject enrollment, an eGFR test must be read to confirm that levels do not indicate compromised kidney function. This test will done to confirm eligibility of the patient, but will be repeated at the 12 month study visit in order to maintain proper kidney functioning if randomized to the treatment group.

After consent and HIPAA forms have been signed, the patient will then be eligible for randomization. It is important for study investigators to emphasize prior to consent that every patient is randomly selected to be in one of two study groups: treatment or observation. The patient will be randomized at the time of enrollment, and the study population will be randomized in a 1:1 ratio. If the study subject is randomized to the treatment group, s/he will receive a prescription for Metformin from the study investigator at this visit or after the investigator receives results from the blood test if recent creatinine levels are not available in the patient's chart. If the patient consents to be a part of the optional genetic research, a 0.6 tsp blood draw will be performed to measure baseline genetics before study procedures begin.

CHAPTER 3: TREATMENT AND FOLLOW-UP

3.1 Treatment Group

The treatment group is the experimental group that will be taking Metformin twice daily for 18 months. Subjects in this group will begin taking Metformin at a dose of 500 mg per day for the first week of the study, 500 mg twice daily for the second week of the study and finally they will increase the dosage to 1000 mg twice daily (1000 mg taken in the morning and 1000 mg taken in the evening). This stepwise increase in dose has been shown to mitigate gastrointestinal distress or discomfort, a side effect of metformin that usually resolves on its own after the first few weeks of taking the drug. The final dose of 2000 mg per day will not change until the 18th month of study, unless GI side effects become intolerable to any individual study subjects. In the event that this occurs, dosage will be adjusted such that the subject's side-effects subside. At 18 months, subjects will stop taking Metformin.

3.2 Observation Group

One half of the study subjects will be assigned to the observation group. This group will receive no treatment for their AMD, and must not receive intraocular medication during the 18 month interventional study period. Because there are currently no treatment options for patients with dry AMD and thus standard of care is to observe the progression of these patients, randomization of study subjects to the observation group is ethical since no care is being withheld. If a patient in this study group develops neovascularization for which their ophthalmologist advises treatment, the subject will exit the study in order to ensure that his or her care is not compromised.

3.3 Compliance

Study subjects will receive a call from study personnel 1 week post-enrollment to ensure that s/he has obtained their metformin from the pharmacy if s/he is in the treatment group and to encourage compliance. As a part of standard of care, clinic staff will also call patients prior to each clinic visit to remind them of their upcoming exams.

3.4 Follow-up visit Schedule

Study subjects will have a total of 5 ophthalmic exams during which information and images are collected and used in this study, at time point 0 months (enrollment), 6 months, 12 months, 18 months, and 24 months. The interventional portion of the study will last 18 months. All subjects in the treatment group will stop metformin use at 18 months. All study subjects will then come for a final visit at 24 months where normal study follow-up testing will be completed. These are timed specifically such that they are a part of each patient's standard of care schedule. Thus, no extra visits are required for subjects enrolling in this study.

3.5 Follow-up visit Testing Procedures

Each exam will include standard ophthalmic work-up, including the evaluation of visual acuity using ETDRS and low luminance testing using a neutral density filter. ETDRS testing will be optional for those subjects presenting without geographic atrophy smaller than 1.25 mm^2 (0.5 Macular Photocoagulation Study disc areas) in size. Furthermore, at each exam fundus autofluorescence imaging, optical coherence tomography (OCT), and fundus photography will be done to monitor these patients' AMD as a part of standard of care. These are the same images that will be used to assess change in area of GA and the volume of drusen. In addition, during the first study exam (month zero) and month 18 exam, each patient will be asked to complete the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25), a 25 question survey of visual function and quality of life developed by the NEI and the Low Luminance Questionnaire, a 32 question survey used for assessing self-reported vision problems under low vision and at night. To confirm that a study subject's kidney is functioning properly and to remain in accordance with FDA regulations, an eGFR test will be done at enrollment and at 1 year (month 12).

If site resources allow and the patient consents, a blood test will be done at the enrollment visit and at month 18. 0.6 tsp of blood will be drawn from the patient in order to perform un-biased next generation sequencing on the specimen in order to identify any patterns in gene activation among different groups of patients so that novel disease mechanisms and/or therapeutic avenues can be identified and further explored.

3.6 Specimen Banking Procedures

In the optional section of the informed consent form, the subject will have the opportunity to consent to two additional blood tests, one at the enrollment visit and the other at the 18 month visit. The specimens will be banked at 400 Parnassus Avenue San Francisco, CA 94143. The specimens will be stored indefinitely unless instructed to destroy the specimens by the subject in writing to 400 Parnassus. The anticipated future research is concretely undecided; however, it will be a genetic analysis of the patients with the hopes of identifying novel disease mechanisms that will translate to therapeutic avenues. The specimens will be stored with a unique study ID that contains no identifiers tracing back to the subject. The freezer is stored in a locked room with limited key access. The bank is unfunded therefore its longevity is not ensured. Should the PI leave the institution the specimens from this study will be destroyed immediately thereafter.

CHAPTER 4: MANAGING RISK

4.1 Safety: The Use of Metformin in Non-diabetic Patients

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects nor is there any accumulation of metformin in either group at usual clinical doses (36). Additionally, although the drug is indicated for use in diabetics to lower blood sugar, several studies have been conducted involving the use of Metformin in non-diabetic patients. It has been safely studied with few adverse effects in non-diabetic populations to assess its effect on weight loss, cancer treatment, polycystic ovary syndrome, and more (37, 38). In fact, metformin is now recommended by the American Diabetes Association for prevention of diabetes in pre-diabetic populations (39). Finally, in a study done by Bannister et al (2014), type 2 diabetics on metformin monotherapy had longer survival than matched controls with no DM2, suggesting the potential for metformin to convey benefits in both populations (40).

The greatest risk for patients taking metformin is the extremely rare but serious side-effect of lactic acidosis. Most reported cases of lactic acidosis occur in patients with compromised renal function. To avoid this risk, we have strict eligibility criteria that disqualify patients who have moderate to severe kidney disease from participating in this study. This is characterized by stage 3 or higher chronic kidney disease. In fact, these criteria are very cautious given recent data suggesting that the contraindication levels should begin at stage 4 and higher CKD (41, 42).

4.2 Risks to Study Subjects

As in all research studies, subjects are at risk for loss of confidentiality. Data to be collected in this study are unlikely to affect reputation, insurability, etc., if they were lost or disclosed. However, standard consequences of loss of privacy, due to patient identifiers being revealed, would result if study data were no longer private. The study investigators and personnel take many measures to ensure that subjects' personal health information remains confidential. This includes storing and transmitting data on secure UCSF servers. Data transmitted to the coordinating center from outside sites will be done in a secure manner, via the use of password protected files. For data that is analyzed outside of locked clinic/office areas, all patients will be identified with a unique identifier, not by name or medical record.

Study subjects randomized to the treatment group face additional risks associated with taking metformin, including the following:

Common side effects of metformin (not severe):

- Diarrhea
- Nausea

- Gas
- Head Pain
- Stomach Cramps
- Swelling of the Abdomen
- Taste Problems
- Vomiting

Infrequent side effects of metformin (not severe):

- Chills
- Dizzy
- Excessive Sweating
- Fingernail and/or Toenail Disease
- Flu-Like Symptoms
- Heart Throbbing or Pounding
- Incomplete or Infrequent Bowel Movements
- Indigestion
- Inflammation of the Nose
- Muscle Pain
- Rash
- Temporary Redness of Face and Neck
- Inadequate Vitamin B12

Infrequent side effects of metformin (severe):

- Trouble Breathing

Rare side effects of metformin (severe):

- Increased Blood Acidity due to High Levels of Lactic Acid (Lactic acidosis)
    - Intravascular administration of iodinated contrast media to patients who are taking metformin can result in lactic acidosis, only if the contrast medium causes renal failure and the patient continues to take metformin in the presence of renal failure.[44]
- Low Blood Sugar
- Megaloblastic Anemia
- Reaction due to an Allergy
- Drug-drug interactions with other cationic drugs such as:
    - Procainamid
    - Digozin
    - Quinidine
    - Trimethoprim
    - Vancomycin
    - Cimetidine[45]

LABEL WARNING:

- Lactic Acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE or GLUCOPHAGE XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur

in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. (36)

4.2.1 Withdrawal of Study Subjects

Study subjects have the right to withdraw from this study for any reason, at any time. If a subject indicates that s/he wants to withdraw from the study, the investigator personally should attempt to speak with them to determine the reason. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document.

In addition, the investigators will discontinue patients from the study treatment or the study or both in the following circumstances:

- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- The investigator decides that the patient should be withdrawn from the study. If a SAE or a clinically significant laboratory value is the basis for this decision, the investigator will discontinue the study therapy and take appropriate measures. The investigator must immediately notify the study sponsor.
- The patient or attending physician requests withdrawal of the patient from the study.
- The investigator or the study sponsor stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The study therapies have shown unacceptable toxicity, such as lack of recovery of more than 4 weeks since last study treatment dose.
- The patient becomes pregnant or fails to use adequate birth control (for women with reproductive potential).
- The patient is noncompliant with study procedures.

4.2.2 Reporting Adverse Events

During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any adverse events. For 30 days after the last dose of oral metformin is

taken patients should be closely followed for study treatment-related adverse events in order to detect delayed toxicity. If treatment-related toxicity is present beyond 30 days post last treatment, patients must be followed every 30 days until the toxicity resolves, another therapy is initiated, or death.

If a patient experiences an adverse event after the ICD is signed but the patient never receives study specific metformin treatment the event will ONLY be reported if the investigator believes that the event may have been caused by a protocol procedure. In addition, all AEs occurring after the patient receives the first study specific metformin treatment must be reported to the UCSF CHR via the CRF.

The Investigators will report to the CHR their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug via the CRF. For each adverse event recorded on the Adverse Event CRF, the investigator will make an assessment of seriousness, severity, and causality. For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product/therapy, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a therapeutic treatment, whether or not considered related to the treatment
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to the study DSMB and UCSF CHR via the CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Events leading to the clinical outcome of death from progressive disease will be included as part of the safety and efficacy analyses for this study, and will not be recorded as adverse events unless the investigator believes that the event may have been caused by the study treatment.

Serious adverse event (SAE) collection begins after the patient has signed informed consent and has received study treatment. If a patient experiences an SAE after signing informed consent, but prior to receiving study treatment, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert the CHR of any SAE within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms.

An SAE is any adverse event from this study that results in one of the following outcomes:

- death (excluding death due to progression of study disease, unless related to study drug)
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events (SAEs) occurring after a patient has taken the last dose of study drug will be collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug, or drug delivery system, or a protocol procedure.

Any SAE occurring prior to enrollment that the investigator believes may have been caused by a protocol procedure must be reported to the study sponsor or its designee within 24 hours of investigator awareness of the event and recorded on the CRF.

Study-specific clinical outcomes of death from progressive disease should be reported as SAEs only if the investigator deems them related to use of the study treatment. Hospitalizations for the purpose of study-specific interventions are also not considered SAEs or AEs.

IMMEDIATE REPORTING REQUIREMENTS

From Investigator to CHR:

Certain events require immediate reporting to allow the CHR to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the CHR immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the CHR within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the CHR immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

Investigator Follow-Up:
The investigator should follow all unresolved treatment-related adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, new therapy is initiated, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be linked to trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event CRF and in the patient's medical record to facilitate source data verification (SDV). If, after follow- up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event CRF.

INTERIM ANALYSIS
Interim analyses of efficacy are not planned for this study.

DOSE MODIFICATIONS
Doses of metformin will remain at 2000 mg/day unless minor side-effects, namely GI discomfort or distress, become intolerable to the patient. In the event that this is the case, the dose will be decreased to the point at which these side-effects subside.

4.2.3 Discontinuation of Study

The study may be discontinued by the study PI or the Data and Safety Monitoring Board prior to the preplanned completion of enrollment and follow-up for all subjects in the event of unforeseen adverse outcomes affecting the safety of study subjects.

4.3 Data Safety Management Board

Because this study is defined as "greater than minimal risk," IRB protocols require the establishment of a Data Safety Management Board (DSMB). This board is responsible for oversight of this study.

Composition:

Jeremy Keenan, MD
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Associate Professor of Ophthalmology at UCSF and the Proctor Foundation, specializing in cornea and uveitis
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Director, Section of Uveitis and Vasculitis

Independence: The DSMB members will not participate in the study as investigators, nor will they have conflicts of interest regarding the study or the study drug being tested.
Data: The DSMB will review the medical charts of study subjects to ensure that there has been no addition of medical conditions since enrollment that would deem subjects ineligible for participation. This includes diagnosis or progression of chronic kidney disease with creatinine levels ≥1.5 mg/dL for males and ≥1.4 mg/dL for females, Child's Class C cirrhosis, or New York Heart Association's Class III or IV Heart Failure. If any ineligibility factors are met, subjects will be withdrawn from the study to protect their health. Furthermore, if a subject develops neovascularization requiring intervention with intravitreal drugs as evident from fundus photos taken at follow-up exams, the subject will be withdrawn from the study to avoid confounding factors that may affect progression of Geographic Atrophy. This will be monitored by study investigators but also confirmed by the DSMB.
Frequency of Review: The DSMB will formally meet twice during the course of this study, but will be continuously monitoring for adverse events throughout the duration of the study. These meetings will occur when we have hit 25% of our target accrual number, and then again when 75% accrual has been reached.
Authority: The DSMB will have the authority to recommend changes in the study on the level of individual patients and in regards to the study overall. They also hold the power to advise discontinuation of the study in the event that patient safety is compromised via study participation.

4.4 Study Costs

This is an unfunded study. As such, study subjects or their insurance carriers assume the responsibility of paying for a prescription for Metformin HCl for the entirety of the study duration (18 months), should the subject be randomized into the treatment group. All other examinations and procedures during which information and images are captured and analyzed for this study are standard of care practices. As such, the patient or patient's insurance carrier would be covering the cost of these items whether or not s/he is enrolled in this study.

CHAPTER 5: SAMPLE SIZE APPROXIMATION AND STATISTICAL ANALYSIS

5.1 Sample Size Calculation

According to Yehoshua et al (2014) the changes in mean square root area of GA independent of starting size over 26 weeks were 0.19 ± 0.12 and 0.18 ± 0.15 for treatment and control groups respectively (43). Over 52 weeks these were 0.37 ± 0.22 and 0.37 ± 0.21 for treatment and control groups respectively. Extrapolating from the 6- and 12-month data for the control group,

at 18 months one would expect the progression of change in mean square root area to be 0.55 (±0.3 SD). Given this mean and standard deviation, 90 participants with GA (45 per group) would provide 80% power to determine effect size of 33% (ie, 0.55 vs 0.37), assuming a two-sided alpha of 0.05. To account for an estimated 10% drop-out rate, we have rounded this number for patients with GA greater than 1.25 mm^2 (0.5 Macular Photocoagulation Study disc areas) to N=100, with 50 subjects in each group. We include in our total study group an additional 86 subjects without GA greater than 1.25 mm^2 (0.5 Macular Photocoagulation Study disc areas); this is based on the following rationale: we assume progression in the composite dry AMD endpoint (described below) of 72% over 18 months, based on a rate of 60% progression over 1 year (47) , which would correspond to 72% over 18 months (calculation: 40% of patients do not progress in the first year; then 60% of those patients will progress during year 2 (and thus 30% during months 12 to 18), for an 18-month progression rate of: 60% + (40% * 30%) = 72%). We then assume that treatment reduces progression to 40% over 18 months instead of 72% for controls. With power 80% power and alpha 0.05, we would need 39 patients per group (Stata code: power logrank .28 .60, power(0.8)). Multiplying by 1.1 to account for 10% loss to follow-up yields 43 subjects per group, for a total of 86 patients without GA greater than 1.25 mm^3.

5.2 Primary Outcome Measure

- For patients with GA greater than 1.25 mm^2 (0.5 Macular Photocoagulation Study disc areas):
    - We will measure the rate of change in area of geographic atrophy as determined by masked readers of fundus autoflorescence images. To measure this, we will calculate the growth square root of area (mm). Previous studies have demonstrated that taking the square root of area measurements before calculation of enlargement rates of GA removed the dependence of growth on baseline area and resulted in a homogeneous test-retest variance across the range of lesion sizes (43).
- For patients without GA greater than 1.25 mm^2 (0.5 Macular Photocoagulation Study disc areas):
    - We will track a composite outcome measure consisting of prevention of drusen growth (drusen volume increase), prevention of GA development, and prevention of macular neovascularization development (47) over the course of the study period, as determined by masked readers of optical coherence tomography images.

5.3 Secondary Analyses

- Prevention of drusen growth (increase in drusen volume) without progression to GA or macular neovascularization (47).
- Changes in best corrected visual acuity (BCVA) over the study period between the treatment and observation groups
- Comparison of changes in scores over the study period on the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) between treatment and observation groups
- Ocular safety will be assessed at each follow-up exam

CHAPTER 6: REFERENCES

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