Efficacy of Dapagliflozin in the Progression of Geographic Atrophy secondary to Age-Related Macular Degeneration

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A Introduction

A1 Study Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50 years of age in the United States. Dry AMD is a specific form characterized by lipoprotein-rich deposits that form under the retina. With disease progression, in some patients dry AMD progresses to an atrophic form of disease called geographic atrophy (GA). GA is slowly progressive and can lead to vision loss. Recent literature has demonstrated that SGLT2 inhibitors (SGLT2i) such as dapagliflozin can target the ApoM/S1P pathway, increasing activity under inflammatory conditions. Apolipoprotein M is a lipoprotein associated with high-density lipoprotein (HDL). Dysregulated cholesterol efflux (CE) and reverse cholesterol transport (RCT) are critical in AMD pathogenesis. ApoM may have beneficial effects on dry AMD through its regulation of CE and RCT. The current US FDA-approved treatments for GA, a C3 or C5 complement inhibitor, have shown only modest efficacy, but they are associated with risks including retinal vasculitis, a 2-3-fold increase in chance of conversion wet AMD, and risk of infectious endophthalmitis associated with the monthly or bimonthly injections to maintain efficacy. Due to these concerns, many physicians, including those at Washington University, are currently hesitant to adopt this treatment and are looking for new treatment options to slow the progression of GA. The purpose of this study is to assess the effect of oral SGLT2i dapagliflozin on the progression of GA. This study will consist of a prospective, interventional randomized double-blind placebo-controlled study of patients with advanced dry AMD (as evidenced by presence of GA) who will be randomized to either dapagliflozin or placebo. Patient demographics and baseline ocular health will be recorded, and comprehensive ocular examination coupled with various ophthalmic imaging modalities and visual function tests such as ultra-wide field fundoscopic photos, fundus autofluorescence, optical coherence tomography (OCT), dark adaptation, and will be taken at the initial visit, 6 months, and 1 year. Primary outcome of interest will be progression of GA lesion area over the 1-year period, and secondary outcomes include structural and functional testing for visual function such as change in drusen volume as measured by OCT, dark adaptation, and low luminance BCVA to determine the effect of dapagliflozin on the progression of dry AMD.

A2 Primary Hypothesis

The primary hypothesis is that the rate of progression of the GA lesion over one year (as measured by FAF will be decreased post-dapagliflozin intervention.

B Introduction

B1 Prior Literature and Studies

Age-related macular degeneration (AMD) is a condition characterized by the gradual deterioration of the macula, a small central area of the retina responsible for sharp vision. It predominantly affects individuals over 50 and is the leading cause of blindness

in developed countries (Apte et al. 2018). In the United States, approximately 6% of those aged 65-74 and 20% of those over 75 are affected by AMD (Leibowitz et al., 1980). Given the global increase in life expectancy, the elderly population is projected to grow substantially in the upcoming years (Ortma & Velkof, 2014). To be sure, according to U.S. Census Bureau projections, the number of Americans over 65 will more than double, reaching 80 million by mid-century (Day, 1993). Unless effective prevention or treatment strategies are implemented, the incidence of AMD cases leading to visual impairment is expected to rise with the aging population.

AMD is divided into two primary subtypes: non-neovascular ("dry") and neovascular ("wet"). Non-neovascular dry AMD constitutes approximately 90% of cases and is characterized by a gradual degeneration of the macula. Over time, this can lead to the atrophy of the central retina, culminating in central vision loss. Neovascular AMD, although less common, is more likely to cause sudden and often significant central vision loss (Holz et al., 2014). Dry AMD significantly contributes to moderate and severe central vision loss and is typically present in both eyes (Maguire & Vine, 1986; Potter & Thallemer, 1981; Sarks et al., 1988; Schatz & McDonald, 1989; Sunness et al., 1999). In dry AMD, the macula experiences a thinning of the retinal pigment epithelial cells (RPE), along with other age-related changes in adjacent retinal layers (Holz et al., 2014). It is characterized by the presence of drusen, yellow crystalline deposits that form beneath the RPE (Holz et al., 2014). In severe cases, dry AMD leads to noticeable thinning and/or atrophy of the macula, resulting from the loss of RPE and associated capillaries (choriocapillaris). This advanced stage of dry AMD is known as geographic atrophy (GA). The progressive deterioration of light-sensitive photoreceptor cells in GA leads to severe visual impairment in affected eyes. In some cases, dry AMD can transition into the wet form of the disease, which can similarly lead to faster progression of vision loss (Holz et al., 2014).

B2 Rationale for this Study

Although early or intermediate dry AMD is the most prevalent form of the disease, there is currently no approved therapy available. The absence of treatment options for dry AMD is a pressing unmet medical need, and a significant concern for the growing elderly population. For advanced AMD, current therapies, including anti-VEGF pharmacotherapy for neovascular AMD, and new complement pathway antagonists for geographic atrophy come with notable side effects such as potential choroidal neovascularization and intraocular inflammation with pegcetacoplan. Treatments for neovascular AMD and GA are associated with a procedural risk of infectious endophthalmitis. This creates a substantial treatment gap in preventing the progression of geographic atrophy and subsequent vision loss.

Extensive research, including studies conducted by our group, has identified cholesterol accumulation as a key factor in the development and progression of AMD. Additionally, we have found significantly lower serum levels of ApoM in AMD patients. When comparing serum ApoM levels in patients without AMD (n = 944) to those diagnosed with AMD in either one or both eyes, be it dry or wet AMD (n = 53), we observed markedly lower levels in AMD patients (Mann-Whitney test; $p<0.0001$).

Despite recognizing the role of lipid accumulation in driving disease progression and vision loss, no treatments currently exist for addressing the root cause of cholesterol

buildup in AMD. Recent work at Washington University by the Javaheri laboratory has unveiled a link between SGLT2i and ApoM. ApoM, primarily produced by the liver and to a lesser extent by the kidney, directly binds to sphingosine-1-phosphate (S1P) (Christoffersen et al., 2011), a bioactive lipid that activates G-protein coupled receptors (S1P receptors) present in various cell types, including RPE cells. ApoM exerts multiple effects, including antioxidant and anti-atherogenic properties (Elsoe et al., 2012; Christoffersen et al., 2008))) regulation of inflammation, endothelial protection (Christoffersen et al., 2011; Christensen et al., 2016) and cell survival (Ruiz et al., 2017). The Javaheri laboratory has identified ApoM as a regulator of lysosomal function and autophagy in the murine heart (Guo et al., 2023). Further studies have shown that in patients diagnosed with acute COVID-19, randomization to SGLT2i increased ApoM levels (Ripoll et al., in review). Further, ApoM is known to promote macrophage cholesterol efflux (Yao et al, Wolfrum et al.). Despite the existing knowledge linking ApoM to reverse cholesterol transport, lysosomal function, and autophagy, there is limited understanding of ApoM's role in eye diseases and AMD.

Dapagliflozin, a commonly used sodium-glucose co-transporter inhibitor (SGLT2) inhibitor in chronic heart failure, chronic kidney disease, and diabetes, has garnered interest due to its substantial cardiorenal protective effects in these patients. SGLT2 is the major transporter responsible for renal sodium and glucose reabsorption in the proximal convoluted tubule of the kidney. Additionally, SGLT2 inhibitors have pleiotropic effects that favorably impact various processes, including energy metabolism, endothelial function, oxidative stress, inflammation, and autophagy (Bonnet and Scheen 2018, Solini et al 2017, Kim et al 2020, Maayah et al 2020, Ghanim et al 2020, Lambers Heerspink et al 2013, Solini et al 2017).

In multiple experimental systems, including heart failure models and doxorubicin administration, the Javaheri laboratory has demonstrated that SGLT2 inhibitors like empagliflozin and dapagliflozin increase circulating ApoM levels (Guo et al 2025). To date, the use of SGLT2 inhibitors has not been explored as a therapeutic option for slowing the progression of dry AMD. Consequently, this study could significantly broaden our options for slowing the disease progression and mitigating the devastating vision loss associated with dry AMD. Therefore, we hypothesize that dapagliflozin, a potent, highly selective, and orally active inhibitor of human renal SGLT2, holds the potential to slow the progression of advanced dry AMD and delay the onset of debilitating blindness.

C Study Objectives

The objectives of this study are to evaluate the safety and efficacy of dapagliflozin, an SGLT2 inhibitor, administered orally in subjects with geographic atrophy secondary to dry age-related macular degeneration (AMD).

C1 Primary Aim

Primary Efficacy Endpoint:

Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, 6 Month Visit, and 12 Month Visit

C2 Secondary Aim

Secondary Efficacy Endpoint include:

1) The mean change in size of drusen volume from Baseline to 12 Month Visit

2) The mean change in best corrected visual acuity (ETDRS letters) from Baseline to 12 Month Visit

3) The mean change in rod intercept time on dark adaptation from Baseline to 12 Month Visit

4) The mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to 12 Month Visit

C3 Rationale for the Selection of Outcome Measures

In advanced stages of dry AMD, using surrogate markers or anatomical indicators can be beneficial if they accurately represent visual function or predict future vision deterioration. For geographic atrophy (GA), the advanced phase of dry AMD, the degeneration of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris typically advances from the parafovea to the fovea, resulting in significant vision loss. Therefore, preventing the expansion of GA towards the fovea offers promise for preserving central vision. Precise measurement of GA area and reliable projections of its growth have led the FDA to consider reduced progression of GA enlargement as a suitable substitute primary endpoint for GA-focused clinical trials. Techniques like fundus autofluorescence are commonly utilized for lesion area analysis in GA assessment, and the rate of area growth has shown significant connections with GA progression. Some studies have suggested that applying a square root transformation to GA measurements can lessen the correlation between initial measurements and growth rate, thus allowing for a better association with GA progression (Abidi et al.).

Furthermore, the choice of secondary outcome measures is aimed at evaluating both the structural and functional aspects of dry AMD. In dry AMD, conventional visual acuity (VA) has traditionally served as the primary measure. However, in early AMD, VA often remains unaffected and doesn't accurately reflect the severity of the condition. Additionally, typical AMD indicators like drusen accumulation do not consistently correlate with VA. Moreover, drusen can regress spontaneously without discernible functional consequences. Additionally, VA decline is gradual and typically becomes evident in the later stages of advanced dry AMD. Given these considerations, while VA and drusen volume may not be a sufficient primary endpoint for clinical trials focused on dry AMD, they may still be valuable as a secondary measure (Abidi et al.). Currently, there's no established functional vision assessment that has been validated for use as a primary endpoint in dry AMD trials. Thus, we plan to utilize functional capacity measures in dry AMD, such as dark adaptation, best corrected visual acuity, and low luminance best corrected visual acuity, as secondary endpoints.

D Investigational Agent

D1 Preclinical Data

Dapagliflozin is an FDA approved drug with a new drug application (NDA) that explains in more detail the preclinical and clinical information. Broadly, this information below is cited from this NDA on its page 23:

"During the first review cycle, the nonclinical studies did not identify a carcinogenic hazard associated with dapagliflozin. However, due to an imbalance in bladder cancer that did not favor dapagliflozin in the Applicant's clinical program, the Agency recommended that the Applicant conduct additional nonclinical studies focused on evaluating potential bladder tumor promotion with dapagliflozin in a rodent model. In this NDA resubmission, the Applicant submitted additional nonclinical studies that addressed whether dapagliflozin or its major metabolite (dapagliflozin 3-O-glucuronide) directly promoted tumor growth of human bladder tumor cell lines in vitro or in vivo (xenograft studies). Although the Applicant retrospectively demonstrated that dapagliflozin did not induce a transcriptional profile typical of tumor promoters in various rat tissues, the bladder was not among the tissues profiled. Additionally, the Applicant demonstrated that varying glucose concentrations in growth medium did not alter the growth in transitional cell carcinoma cell lines, and that hyperplastic bladders were not observed in a SGLT2 knockout mouse model. The results of these studies were consistent with what the Agency had already concluded (i.e., dapagliflozin did not appear to be a direct tumor promoter or inducer). However, these studies did not address whether dapagliflozin may act as a tumor promoter through changes in urinary volume, flow, and composition within the microenvironment of the bladder. Since the CRL, the Agency has repeatedly recommended acceptable models for evaluating transitional cell tumor growth within the bladder (e.g., transplanting human bladder tumor cells to mouse bladders [orthotopic models] or selectively inducing bladder tumors in rodents in which a genotoxic agent had been administered, such as hydroxybutyl nitrosamine [BBN]). These studies were never conducted. However, at the December 12, 2013 EMDAC meeting, the Applicant stated that they are currently working with experts in the field and are committed to conducting these studies. (NDA)

D2 Clinical Data to Date

Sources of clinical data are similarly cited in the NDA of dapagliflozin on page 25-28. Below is an excerpt from the NDA regarding the clinical data for dapagliflozin:

"The dapagliflozin clinical development program consisted of 37 Phase 1 studies (26 from the original NDA submission and eleven new studies in the 30-MU) and 26 Phase 2b and Phase 3 clinical trials (fifteen from the original submission, plus six new core studies and five supportive studies in the 30-MU). A description of the Phase 2b/3 clinical development program is presented in Table 3. These trials included diverse populations of patients with T2DM. There were drug-naïve patients at an early stage of disease and patients taking oral antidiabetic agents and/or insulin at later stages of the disease. The effects of dapagliflozin were also evaluated in patients with moderate renal insufficiency, established cardiovascular disease, and hypertension. Integrated safety datasets from 21 of the 26 studies were included in the 30-MU. Review of these 21 trials (referred to as the All Phase 2b/3 study pool from this point forward) comprises the main safety review for this NDA resubmission. These trials are identified in the table below."

D3 Dose Rationale and Risk/Benefits

3.a Benefit/Risk and Ethical Assessment

Dapagliflozin has global marketing approval in more than 90 countries. More detailed information about the known and expected benefits and risks and reasonably expected

AEs of dapagliflozin may be found in the Investigator's Brochure. The following is a summary of benefit-risk considerations relevant to the dry AMD population.

3.b Potential Benefits to Subjects

All patients in the study are expected to be treated optimally according to background local standard of care therapy, including treatments to control co-morbidities. Dapagliflozin or matching placebo will be administered in addition to these treatments. These patients will receive close medical attention at clinic visits, irrespective of blinded treatment allocation. The direct benefits to participation in the study may be a slowing of the progression of dry-AMD to preserve central vision longer if the medication proves to efficacious, though patients will be informed that they may be randomized to a group that does not have the medication (placebo group). There may be a possible benefit of improvement in visual acuity, low luminance visual acuity, or dark adaptation for the patient.

3.c Potential Risks to Subjects

The safety profile of dapagliflozin is already well established from prior clinical studies in various clinical settings. These studies have demonstrated that dapagliflozin is generally safe and well tolerated.

Dapagliflozin, as an inhibitor of SGLT2, increases urinary glucose excretions, which is commonly believed to increase the risk of urinary tract infections. Urinary tract infections have been reported in dapagliflozin-treated patients in a slightly higher proportion than in placebo-treated patients in some global Phase III studies, although the rates of urinary tract infections (and serious urinary tract infections) observed in large clinical trials of dapagliflozin and other SGLT2i have been similar to placebo (Wiviott et al 2019, McMurray et al 2019). Increased urinary glucose excretion may also lead to an increased risk of developing genital infections. Genital infections are considered common side effects (in ≥1/100 to <1/10 patients).

Dapagliflozin reduces BP and may reduce blood volume from its diuretic effect, though this could also be an important mechanism of a potential treatment effect. A pooled analysis of patients with T2DM and HF in the dapagliflozin development program, showed no increase of volume depletion events, but an increase in renal events, mainly creatinine increases, in patients treated with dapagliflozin (n=171) compared with patients treated with placebo (n=149). About half of the patients were on loop diuretics (Kosiborod et al 2017). In the dapagliflozin T2DM program, the rate of events related to volume depletion and impaired renal function has been similar between dapagliflozin and placebo.

Dapagliflozin has not been shown to induce hypoglycemia in non-diabetic patients. In clinical pharmacology studies, healthy subjects have been treated with single oral doses of up to 500 mg and multiple oral doses of 100 mg up to 14 days without any hypoglycemic events. However, in patients with T2DM and on insulin or sulfonylurea medication, there is an increased risk of hypoglycemia. Patients with T2DM will be monitored in the hospital as part of standard of care, which in North America, Latin America, Europe, and India includes blood glucose monitoring.

There have been reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin and other SGLT2 inhibitors. Diabetic ketoacidosis is considered a rare (in ≥1/10000 to <1/1000 patients) adverse drug reaction for dapagliflozin in patients with T2DM.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, interruption of dapagliflozin treatment should be considered, and the patient should be evaluated promptly.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements caused by infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in patients in these circumstances.

Since this protocol suggests utilizing dapagliflozin in a new patient population, the risk profile is best addressed by calling attention to the strong safety profile seen in the large-scale, long-term randomized controlled trials. The DECLARE-TIMI 58 trial, which included 17,160 patients with type 2 diabetes, stratified results by age, included patients ≥65 and ≥75 years old. The study found no increased risk of major adverse cardiovascular events (MACE), fractures, and hypoglycemia compared to placebo (Wiviott et al., 2019). Notably, dapagliflozin did not increase hypoglycemia risk, making it a safer alternative to sulfonylureas or insulin in older adults, who are at higher risk of falls, cognitive decline, and frailty-related complications (Perkovic et al., 2019). Additionally, the DAPA-HF trial confirmed no excess risk of renal decline, hypotension, or ketoacidosis in older adults with heart failure, further supporting the cardiorenal safety of dapagliflozin in aging populations (McMurray et al., 2019). Diabetic ketoacidosis (DKA), a rare but serious adverse event, has not been significantly observed in non-diabetic populations, making dapagliflozin a viable candidate for expanded indications beyond diabetes. In a pooled analysis of 15 Phase I-III trials, empagliflozin did not show any increased incidence of any adverse events, and this data based on >15,000 patient-years' exposure supports the favorable benefit-risk profile of SGLT2 inhibitors. (Kohler et al. 2017). Finally, pooled analysis of 9 Phase III studies confirmed that long-term use (104 weeks), which exceeds this study design of 52 weeks, in elderly patients did not lead to excess dehydration, renal complications, or severe genitourinary infections (Fioretto et al., 2016).

Given its robust clinical trial data, real-world safety evidence, and broad regulatory acceptance, dapagliflozin is well-positioned for experimental expansion in safe use in aging populations, such as those populations that have geographic atrophy.

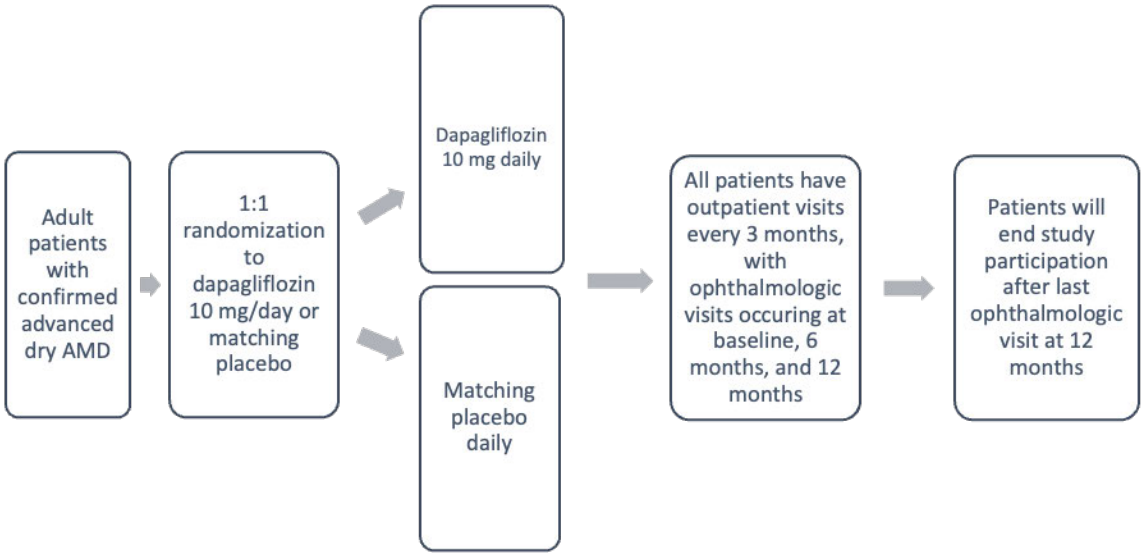
Pupillary dilation will be performed using 1% tropicamide and 2.5% phenylephrine, standard mydriatics in clinical and research settings. While generally safe, side effects of pupillary dilation may include temporary blurred vision, difficulty with near focus, light sensitivity, and mild irritation for several hours. The most serious risk is acute angle-closure glaucoma in individuals with narrow angles. AMD patients often receive pupillary dilation every 6 months as per standard of care, which is the frequency for this study.

Nevertheless, all participants will be screened beforehand, and potential risks will be discussed during the consent process.

E Study Design

E1 Overview or Design Summary

This is a single-center, parallel-group, randomized, double-blind, placebo-controlled, Phase II trial in approximately 70 adults with dry advanced AMD or geographic atrophy. The study is evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily by mouth for 1 year in addition to background local standard of care therapy, including treatments to control co-morbidities. Patients should start study drug the same day as randomization.



E2 Subject Selection and Withdrawal

In this study, patients will be recruited from sites with adult patients at outpatient clinics of retina specialists at the Retina Clinic at Barnes Jewish Hospital Center for Outpatient Health. Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study to be randomized to study drug. Under no circumstances can there be exceptions to this rule. Patients' eligibility criteria may be reassessed on one subsequent day following the initial Screening/Baseline Visit. However, if they still do not meet the inclusion criteria after this reassessment, they must be considered screen failures.

In this study, "enrolled" patients are those who sign the consent form. "Randomized" patients are those who undergo randomization and receive a randomization number. Withdrawal can occur at any time during the study.

2.a Inclusion Criteria

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
2. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures
3. Participant is male or, if female, participant is surgically sterilized or amenorrheic for at least one year
4. ≥50 years old
5. Evidence of dry advanced AMD with the presence of non-foveal Geographic Atrophy (GA)
   a) The geographic atrophy must not involve the center point of the fovea.
   b) Total area of geographic atrophy must be between 2.5 mm^2 and 17.5 mm^2 (1 – 4 disc areas, respectively).
   c) If the geographic atrophy consists of multiple lesions, at least one lesion must have an area of ≥1.25 mm^2 (equivalent to 0.5 disc areas).
6. BCVA between 20/25 and 20/320
7. Must be treatment-naïve for AMD, except for oral supplements

2.b Exclusion Criteria

Prior investigational drug use within 60 days
Use of other SGLT2 inhibitors
History of symptomatic hypotension or symptomatic hypotension (symptoms of hypotension + SBP < 90mmHg) at baseline
Type I and Type II Diabetes Mellitus
End stage renal disease or estimated glomerular filtration rate less than 25 mL/min/1.73 m2 per MDRD calculation
History of heart failure
History of a serious hypersensitivity reaction to dapagliflozin or any of the excipients in FARXIGA
Other concomitant disease or condition that investigator deems unsuitable for the study, including drug or alcohol abuse or psychiatric, behavioral, or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the study instructions or follow-up procedures
Any prior treatment for AMD (dry or wet) or any prior intravitreal treatment for any indication in either eye, except oral supplements of vitamins or mineral
Any intraocular surgery or thermal laser within 3 months of date of randomization
Any ocular or periocular infection (including blepharitis), or ocular surface inflammation in the past 12 weeks
Any prior thermal laser in the macular region, regardless of indication (self-report)
Any evidence of choroidal neovascularization in study eye
Enrollment in another interventional trial during the trial period

2.c Ethical Considerations

Dapagliflozin has global marketing approval in more than 90 countries. More detailed information about the known and expected benefits and risks and reasonably expected AEs of dapagliflozin may be found in the Investigator's Brochure. The summary of benefit-risk considerations is summarized in Section D3.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements. The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. An IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. If required by local regulations, the protocol should be re-approved by the IEC annually. Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The PI will handle the distribution of any of these documents to the national regulatory authorities and will provide Regulatory Authorities, IRB/IECs and PIs with safety updates/reports according to local requirements. For the United States, the PI is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. The delegate will provide this information to the PI so that he/she can meet these reporting requirements.

2.d Subject Recruitment Plans and Consent Process

The study involves one population of interest that will be randomized to one of 2 arms: intervention with dapagliflozin or placebo. The population is a group of patients >50 years old with advanced dry AMD as evidenced by presence of geographic atrophy secondary to AMD. [redacted] The investigator or coordinator will approach patients during Retina Clinic where these patients are routinely seen for clinical care and either offer to discuss the clinical study or schedule a follow-up phone call to describe the purpose of the clinical study which will be to test the effects of a known FDA-approved drug dapagliflozin on preventing the progression of advanced dry-AMD. The investigator or coordinator will describe that the study entails taking the medication for 1 year to help us inform whether the medication can be used to slow progression of dry-AMD. The study investigator or coordinator will inform the participant that if they consent for the study, a first study screening/baseline visit will be scheduled where the patient will have a routine comprehensive ocular examination along with fundoscopic and OCT imaging and they will be prescribed the medication to be taken every day. The study investigator or coordinator will inform the participant that participation in the study is completely voluntary and that the decision to participate will not influence ongoing clinical care in any way. The additional risks include adverse side effects such as increased risk of genitourinary infections, dehydration, and rarely a serious perineal infection called Fournier's gangrene. The direct benefits to participation in the study may be a slowing of the progression of dry-AMD to preserve central vision longer if the medication proves to efficacious, though patients will be informed that they may be randomized to a group that does not have the medication (placebo group). There may be a possible benefit of improvement of visual function for the patient. The placebo tablets may contain lactose, which may cause gastrointestinal discomfort in lactose-intolerant individuals. Furthermore, participation may eventually help find a

treatment for slowing the progression of dry AMD and its subsequent vision loss. The patient will then be informed that they do not have to decide at that moment, and they will be given a form describing the study and they can schedule a follow-up call at 1 week later if they would prefer more time to consider participation. This will be done in a private space, and the subject will be given ample amount of time to ask questions.

[redacted]

Randomization Method and Masking

Investigator(s) or designee should keep a record (the patient's screening log) of patients.

The Investigator(s) or designee will:

a. Obtain informed consent from the potential patient before any study specific procedures are performed
b. Assign potential subject a unique enrollment number/subject ID
c. Determine patient eligibility as above inclusion or exclusion criteria. Two attempts to meet the randomization criteria is allowed

A centralized randomization in Redcap will be utilized when eligibility of patients is established. The integrated randomization program will use small random permuted blocks of size 4 or 6 and then assign according to a 1:1 randomization to placebo or SGLT2 inhibitor. If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment (note that more than 1 attempt to meet the randomization criteria is allowed). Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should discuss with team members regarding whether to continue or discontinue the patient from treatment.

No member of the extended study team, personnel at study site or the study team handling study data will have access to the randomization scheme during the study. Neither the patient nor any of the Investigator's staff/designee who are involved in the treatment or clinical evaluation and monitoring of the patients will be aware of the treatment received. In the event that the treatment allocation for a patient becomes known to the Investigator or other study staff involved in the management of study subjects, the Investigator must notify the appropriate parties immediately.

2.e Early Withdrawal of Subjects

Patients are free to withdraw from the study at any time (study drug and assessments), without prejudice to further treatment. Withdrawal of consent should only occur if the patient has received appropriate information about, and does not agree to, any kind of further assessments or contact, including modified follow-up options. Discontinuation of study drug is not considered withdrawal of consent.

2.f When and How to Withdraw Subjects

The study may be stopped if patients are placed at undue risk because of clinically relevant findings. In terminating the study, the Investigator or delegate will ensure that adequate consideration is given to the protection of the patients' interests.

2.g Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for follow-up and is unable to be contacted by the study site staff.
The following actions must be taken if a subject fails to return to the clinic for a required study follow-up visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (3 telephone calls and a certified letter to the subject's last known mailing address). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

E3 Study Drug

3.a Description

Dapagliflozin and its matching placebo tablets will be packed in bottles. The tablets may contain lactose, which may cause gastrointestinal discomfort in lactose-intolerant individuals.

3.b Treatment Regimen

At randomization (Day 1), eligible patients will be randomly assigned to 1 of 2 treatments:

- Dapagliflozin 10 mg, given once daily per oral use
- Placebo—one tablet to match dapagliflozin 10 mg, given once daily per oral use

The study drug should be taken by mouth as soon as possible after randomization and then once daily in the morning, at approximately the same time every day, during the treatment period of 1 year. If the patient, for any reason is not administered the study drug in the morning, any other time point during the day may be applied, provided the study drug is routinely administered in approximately 24-hour intervals.

3.c Method for Assigning Subjects to Treatment Groups

All patients will be randomly assigned to study drug a centralized randomization program in Redcap. Randomization to study drug will be performed in balanced blocks to ensure approximate balance between the treatment groups (1:1).

3.d Preparation and Administration of Study Drug

Patients will be randomized 1:1 to either dapagliflozin 10 mg or placebo once daily per oral use by the contracted preparation organization. Every attempt should be made to have patients on dapagliflozin 10 mg or matching placebo during the course of the study. The study drug should be taken as soon as possible after randomization and then once daily in the morning, at approximately the same time every day, during the 12 month treatment period.

3.e Subject Compliance Monitoring

Patients will be asked at each of the pre-defined visits regarding compliance to their medication regimen. Severe non-compliance with the study protocol may result in discontinuation from the study drug.

3.f Prior and Concomitant Therapy

All patients will be treated according to local guidelines on standard of care treatment for dry AMD. Subjects enrolled must be treatment-naïve (no previous treatment for AMD) in either eye except for oral supplements of vitamins and minerals. Any treatment with any investigational agent for any condition in the past 60 days, or treatment with an investigational agent for any condition during the trial, is not permitted.

However, concomitant treatment with open label SGLT2i (e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fixed-dose combinations containing these drugs), is prohibited. Background medications should be part of clinical practice and will not

be provided by the investigator. Medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded.

3.g Blinding of Study Drug

Blinding of the study drug will be ensured using a double-blind technique of matching placebo as managed by the pharmacy. No member of the study team, personnel, or delegates will have access to the randomization scheme during the study.

3.h Receiving, Storage, Dispensing and Return

The study team will maintain a drug accountability log to track the dispensing, use, and return of the study drug. Participants will be instructed to return all unused study drug, empty containers, and partially used doses at each study visit. Compliance with study drug administration will be assessed through pill counts.

The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to the patients.

All study drugs should be kept in a secure place under appropriate storage conditions. The study drug label on the bottle specifies the appropriate storage conditions.

Any study drug deliberately or accidentally destroyed must be recorded. When the study drug is destroyed at site: study site personnel, will account for all study drug at the site, unused study drug, and for appropriate destruction. Certificates of delivery, destruction, and return should be signed.

F Study Procedures

F1 Screening for Eligibility

The population of interest is a group of patients >50 years old with advanced dry AMD as evidenced by presence of geographic atrophy secondary to AMD. The PI and Sub-I's will identify patients who are seen at the practices of Dr. Rajendra Apte, Dr. Kumar Rao, Dr. Kisha Piggott according to the inclusion and exclusion criteria referenced in section 5.2.

F2 Informed Consent

The Investigator or their designated representative will discuss the study's purpose, including its potential risks and benefits, with the participant and address any questions they may have. Participants will be made aware that their involvement is entirely voluntary. They must sign an informed consent form (ICF) that complies with 21 CFR 50, applicable local laws, ICH guidelines, privacy and data protection standards, and the requirements of the IRB/IEC. Consent must be secured before any study-specific activities (e.g., procedures outlined in the protocol) are performed, and this process must be recorded in the participant's source documents. The medical record should note that written consent was obtained prior to enrollment, including the date of consent, and the person obtaining it must also sign the ICF. Participants will receive a copy of the signed ICF.

Only participants who provide IRB/IEC-approved informed consent (witnessed if required by law or regulation) may be enrolled. Details about known common side effects of the investigational treatment, as outlined in the Investigator's Brochure (IB), will be included in the ICF and discussed with participants during the consent process and throughout the study as necessary. Any newly identified safety information about the investigational drug that emerges between IB updates will be shared appropriately—such as through an Investigator Notification (IN) or aggregated safety report—and may necessitate revising the ICF, followed by a discussion with the participant. Declining to participate in these optional assessments will in no way affect the participant's ability to join the main research study. A copy of the signed consent will be given to the participant.

F3 Vital Signs

Vital signs will include measurement of blood pressure and pulse rate.

After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, blood pressure and pulse rate will be measured using an automated device. For virtual visits requiring blood pressure and pulse check, participants will be guided through this process with their home machine.

If SBP is less than 90 mmHg at the at Screening/Baseline Visit (see Exclusion Criteria Section 5.2 of the protocol for details), two additional readings can be obtained, so that up to three consecutive assessments are made, with the participant seated quietly for approximately five minutes preceding each repeat assessment.
In case of repeated vital assessments, the electronic case report form (eCRF) should contain the qualifying results.

For patients whose SBP is measured below 90 mmHg across three consecutive readings, reassessment of the blood pressure may be conducted on a single separate day to reassess eligibility. If SBP is still less than 90 mmHg, patient will be considered a screen fail and will not be eligible for participation in the trial.

Blood pressure measurements should be performed immediately following the informed consent process, and if blood pressure does not meet the inclusion criteria, no additional screening procedures will be conducted.

F4 Medical History

A detailed medical history will be collected by interview and medical record review at the Screening/Baseline Visit to document current medical conditions and allergies. Date of onset for medical conditions will be recorded in the CRFs but can be approximate if detailed records are not available.

F5 Concomitant Medications (Con Meds)

A comprehensive medication history will be collected, covering all current medications, such as prescription drugs, over-the-counter medications, supplements, and investigational products, with details on dosage, duration, and indication. Initiation dates can be approximated if detailed records are not available.

F6 Physical Examination

A targeted physical examination, encompassing an assessment of general appearance, cardiovascular, abdominal, genitourinary, and integumentary systems, will be conducted to evaluate baseline clinical characteristics and monitor for potential adverse events. All findings identified at baseline will be recorded in the Case Report Forms (CRFs), and any findings from follow-up visits that deviate from the baseline and meet the criteria for an adverse event will be reported accordingly.

F7 Local Basic Metabolic Panel (BMP) and Complete Blood Count (CBC)

Approximately 10 mL (equivalent to 2 teaspoons) of blood will be collected for a BMP and CBC analysis run at Barnes Jewish laboratory. The BMP and CBC will be evaluated at the Baseline Visit, the 6 Month Visit, and the 9 Month Visit to monitor key metabolic parameters throughout the study. Additional BMP and CBC assessments may be conducted at the discretion of the Investigator for participants reporting adverse events, as needed to ensure safety and evaluate potential study-related effects.

F8 Study Drug Initial Dispensing and Refill

A 90-day supply of study drug will be initially dispensed at the Day 1 Visit following randomization. The study drug will be dispensed to participants in labeled containers with unique identification numbers. Additional 90-day supplies will be provided by the study team at the 3 Month Visit, 6 Month Visit, and 9 Month Visit. For participants who elect to conduct their 3 Month Visit and 9 Month Visit virtually, study drug will be provided via mail delivery.

Participants will be provided with written instructions for the proper storage and handling of the study drug. The study drug must be stored in its original container at the specified temperature and kept out of reach of children or pets.

F9 Drug Accountability

Participants will be instructed to return all unused study drug, empty containers, and partially used doses at each study visit. Compliance with study drug administration will be assessed through pill counts. Participants who do not take the study drug as instructed or fail to return unused study drug may be withdrawn from the study.

The study site will maintain detailed drug accountability logs, including the quantity of study drug received, dispensed, returned, and destroyed. Any discrepancies in drug accountability will be documented and reported to the IRB as required

Participants must maintain a compliance rate of at least 80% over each assessment period (e.g., between study visits). Compliance is defined as the percentage of doses taken as prescribed out of the total expected doses, calculated as follows:

$$\text{Compliance Percentage} = \left(\frac{\text{Number of Doses Taken}}{\text{Number of Doses Expected}} \right) \times 100$$

If a participant's compliance falls below 80% during any assessment period, the Investigator will counsel the participant on the importance of adherence and provide

strategies to improve compliance (e.g., reminders, support tools). Should the participant fail to achieve at least 80% compliance by the subsequent visit, they will be withdrawn from the study. Withdrawal due to non-compliance will be documented in the participant's Case Report Form (CRF), including the calculated compliance percentage, dates of assessment, and any remedial actions attempted.

F10 Ophthalmologic Exam

A special microscope called a slit lamp will be used to look closely at the anterior parts of the eye like the eyelids, cornea, iris, and lens. To examine the back of the eye, including the retina and optic nerve, pupil dilation will be achieved using 1% tropicamide and 2.5% phenylephrine administered topically, and then the doctor will use a bright light and a handheld lens in a technique called indirect ophthalmoscopy.

F11 Retinal Exam

The retinal exam focuses on checking the back part of the eye, and includes fundus photography, which takes detailed color pictures of the retina to look for signs of disease. It also includes optical coherence tomography (OCT), which creates cross-sectional images of the retina to see the layers of the retina in high detail. Autofluorescence is used with OCT to highlight areas where retinal cells may have subject to stress or damage, helping to detect early signs of diseases in macular degeneration.

F12 Functional Eye Exams

Functional eye exams measure the function of your eyes as opposed to structure, such as how well your eyes see in different lighting conditions. They include tests like dark adaptation, which checks how quickly your eyes adjust to darkness, and low-luminance visual acuity, which measures how clearly you see in dim light—both useful for detecting early vision changes.

F13 Schedule of Measurements

Visit Name	**Baseline [1]**	**Day 1[1]**	**Day 30[5]**	**3 Month[5]**	**6 Month**	**9 Month[5]**	**12 Month (End of Study)**
Visit Windows (Days)	**-14-1**	**1**	**30 (± 3)**	**90 (± 7)**	**180 (± 10)**	**270 (± 10)**	**360 (± 10)**
Informed Consent	X						
Medical History	X						
Inclusion/Exclusion Review	X						
Con Med Assessment	X		X	X	X	X	X
Ophthalmologic Exam[2]	X				X		X
Retinal Exam [3]	X				X		X

Functional Eye Exams[4]	X				X		X
Physical Exam	X				X		X
Study Drug Initial Dispense and Administration		X					
Medication Refill				X	X	X	
Drug Accountability			X	X	X	X	X
Local BMP and CBC	X				X		X
Blood Pressure, HR	X	X	X	X	X	X	X
Adverse Event Assessment	X		X	X	X	X	X

[1] Baseline and Day 1 visits can be completed on the same day
[2] Ophthalmologic Exam includes slit lamp exam, biomicroscopy, indirect ophthalmoscopy with pupillary dilation.
[3] Retinal Exam includes fundus photography and optical coherence tomography (with autofluorescence).
[4] Functional eye exams include dark adaptation and low-luminance visual acuity
[5] 30 Day, 3 Month, and 9 Month Visits are optionally virtual, patient can elect to return in person for a research visit or choose a virtual visit if they can provide a home blood pressure and pulse rate. Refill of study medication will be mailed to participant's home in the case of a 3 or 9 month virtual visit.

F14 Safety and Adverse Events

14.a Definitions of Adverse Events

An Adverse Event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

A Serious Adverse Event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

14.b Classification of Events

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: *http://evs.nci.nih.gov/ftp1/CTCAE/About.html*

To assist with grading of adverse event severity, the following definitions are provided:

Mild = Aware of sign or symptom, but easily tolerated

Moderate = Discomfort enough to cause interference with usual activity

Severe = Incapacitating with inability to work or do usual activity

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:

http://www.hhs.gov/ohrp/policy/advevntguid.html

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the Investigator(s).
When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Investigator would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

14.c Reporting Procedures

All reportable severe adverse events (SAEs) have to be reported, whether or not considered causally related to the study drug. The representative is responsible for informing the IRB/IEC and/or the Regulatory Authority of the SAE as per local requirements.

If any reportable SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate designated representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated representative works with the Investigator to ensure that all the necessary information is provided to the database **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other reportable SAEs.

For fatal or life-threatening reportable SAEs where important or relevant information is missing, active follow-up is undertaken immediately. Site personnel inform the investigator of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness is the Investigator's Brochure for dapagliflozin.

Investigator and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected AEs that occur in accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the Investigator or designated delegate to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines. The conduct of the study will comply with all FDA safety reporting requirements.

PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO. It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than 7 calendar days after initial receipt of the information. A life-threatening adverse experience is defined as any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk within 15 calendar days after initial receipt of this information. A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
    - Death
    - A life-threatening adverse drug experience
    - Inpatient hospitalization or prolongation of existing hospitalization
    - A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
    - Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy and Rheumatology Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 301-796-9728

14.d Adverse Event Reporting Period

Reportable adverse events will be collected from first dose of study treatment through 30 days following the last study treatment.

F15 Study Outcome Measurements and Ascertainment

The objectives of this study are to evaluate the safety and efficacy of dapagliflozin when given to subjects with geographic atrophy secondary to dry age-related macular degeneration (AMD). Primarily, Optos wide-field images with autofluorescence, OCT, AdaptDx^{Tm} dark adaptation, and standard ophthalmic exam will be obtained as per the schedule of measurements in F2.

15.a Primary Outcome Endpoint

Mean rate of change in GA over 12 months measured by FAF at three time points: Baseline, 6 Month Visit, and 12 Month Visit

15.b Secondary Efficacy Endpoints

1. The mean change in size of drusen volume from Baseline to 12 Month Visit
2. The mean change in best corrected visual acuity (ETDRS letters) from Baseline to 12 Month Visit
3. The mean change in rod intercept time on dark adaptation from Baseline to 12 Month Visit
4. The mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to 12 Month Visit

G Statistical Plan

G1 Sample Size Determination and Power

This is a Phase II pilot study (double-masked, placebo-controlled single center clinical trial) evaluating the efficacy of SGLT2 inhibitor dapagliflozin for the treatment of dry AMD. Up to a maximum of 70 patients total (35 patients in each arm) will be randomized with the assumption that 5 in each arm may be lost to follow-up, resulting in 30 evaluable subjects in each arm at the end of the study. Based on the uncertainty of the proportion of patients enrolled who will be evaluable, definitive power analyses are not feasible. Therefore, sample power calculations were performed on a range of possibilities. Assuming the average rate of progression in the year in the control group is ~0.33 mm/year (from GATHER1 trial), we estimate that the effect size that corresponds with a 30% rate reduction is ~0.5 - ~1 based on interpatient variation. A sample size of 30 patients evaluable for the primary endpoint will allow us to detect an effect size of >0.7 with 80% power at two-sided 0.05 alpha. A sample size of 15 evaluable patients will allow us to detect an effect size >1.0. This study is designed to generate preliminary data for future, larger trials rather than confirm hypotheses and, thus, not definitively powering the study is acceptable.

G2 Analysis Plan

2.a Descriptive Statistics

Descriptive statistics will be provided on demographic information, treatment administration, baseline characteristics, and protocol deviations, as well as for selected endpoints at relevant time points. No tests of significance will be carried out to compare treatment groups on baseline data because any observed differences between them must be attributed to chance.

2.b Efficacy Analysis

The efficacy analysis will be conducted on all randomized and treated subjects according to the intention-to-treat principle. For normal endpoints, treatment groups will be compared through an analysis of variance and mixed model for repeated measures including stratification factors.

The overall (one-sided) false positive error rate in this trial, accounting for the conduct of pairwise comparisons with control, is 0.025 for the analysis of the primary endpoint.

2.c Subset Analyses

The trial is not sized to test for the presence of treatment by subset interactions. Thus, true treatment by subset interactions will likely be missed, unless they are quite substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this will not be taken as evidence of a true treatment by subset interaction, given the likelihood that such an observation could be due to chance alone. With these caveats in mind, exploratory subset analyses will be performed to identify any major effect that might be worth testing in future trials. Clinically meaningful subsets will be looked at, including stratification factors.

2.d Safety Analysis

The safety analysis will be conducted on all subjects who had at least one administration of trial drug.

Adverse events will be summarized using MedDRA terms. The incidence and severity of adverse events will be listed and grouped by body system. All laboratory data will be listed and values falling outside normal ranges will be identified. Summary statistics (i.e., mean, median, standard deviation, minimum and maximum) will be presented for all continuous variables. Summary statistics will be given on the number of subjects for whom the trial medication had to be permanently stopped.

G3 Statistical Methods

Data will be analyzed using SAS Studio, SPSS, or R. Descriptive analyses will be performed on baseline, safety and efficacy data. All tables will be created for the treatment arm (dapagliflozin) and overall.

Descriptive statistics will be tabulated as follows:

Categorical data will be summarized in contingency tables presenting frequencies and percentages.

Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, 1st quartile (Q1), 3rd quartile (Q3), and maximum values.

Listings with individual subjects' data will be provided for all CRF (including derived data) and central laboratory data or other external data. Data collected in the CRF that are *not* present in a table will also be listed (e.g. time and method of tonometry, comments fields, data on Fatal Outcomes page, Unscheduled Visit pages, etc.).

The primary efficacy endpoint is mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, 6 Month Visit, and 12 Month Visit. To eliminate the dependency of GA growth rates on the Baseline lesion size (Feuer et al., 2013), instead of using the observed GA area measurement, the square root of the GA area will be used in the analysis. For analyses of the primary endpoint, a Mixed-Effects Repeated Measures (MMRM) model will be used to assess the

differences between the treatment groups in rate of change of GA area over 12 months. Models will be fitted by using restricted maximum likelihood (REML) and include Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. Fixed effects will include treatment, visit, the Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), pattern of FAF at the junction zone of GA (none/focal vs. banded/diffuse), treatment by visit interaction, and the stratification factors by visit interactions. An unstructured (co)variance structure will be used to model the within-subject errors. If this analysis fails to converge, alternative structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The test of the mean rate of change over 12 months will be assessed by testing the appropriate contrast of the model parameter estimates.

Secondary efficacy endpoints are as specified:

- The mean change in size of drusen volume from Baseline to 12 Month Visit
- The mean change in rod intercept time on dark adaptation from Baseline to 12 Month Visit
- Mean change in best corrected visual acuity (ETDRS letters) from Baseline to 12 Month Visit
- Mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to 12 Month Visit

Secondary efficacy analysis will be conducted for intention-to-treat (ITT) population for these pre-specified secondary endpoints. The analyses described above will also be repeated in a supportive manner for the per-protocol (PP) population.

Descriptive tables will be provided for secondary endpoints based on the observed data, but due caution will be exercised in interpreting descriptive tables because of the potential impact of missing data.

Any hypothesis testing performed as part of analyzing secondary efficacy endpoints will be considered exploratory.

For analyses of the secondary endpoints, a similar Model for Repeated Measures (MRM) will be used to assess the differences between the treatment groups at 12 Month visit. The model will be fitted by using restricted maximum likelihood (REML). The model will include Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), size of baseline drusen, and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. Fixed effects will include treatment, visit, the Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), pattern of FAF at the junction zone of GA (none/focal vs. banded/diffuse), treatment by visit interaction, and the stratification factors by visit interactions. An unstructured (co)variance structure will be used to model the within-subject errors. If this analysis fails to converge, alternative structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to

estimate denominator degrees of freedom. Significance tests will be based on appropriate treatment contrasts at 12 Month Visit.

G4 Missing Outcome Data

4.a Handling Missing Data in Efficacy Analyses

Methods that take into account the presence of missing data and that yield valid estimates under the assumption of data missing at random (MAR) will be used. In particular, a Model for Repeated Measures fitted by Restricted Maximum Likelihood method will be used in the primary analysis, whereas-observed data will be used with no imputation.

Of note, the proper approach to address missingness is the prevention of missing data, and efforts will be to be taken to implement proactive approaches to minimize the number of patients who are not assessed at 12 months.

4.b Handling Missing Data in Descriptive Analyses

When summarizing categorical variables, subjects with missing data are generally not included unless otherwise specified. When needed, the category of “Missing” is created and the number of subjects with missing data is presented.

When summarizing continuous variables, subjects with missing data are not included in calculations. No imputations are made.

4.c Handling Missing or Partially Missing Dates

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservative to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

If the partial adverse effect onset date information does not indicate whether the AE started prior to treatment or after treatment, the AE will be classified as after the start of treatment.

G5 Unblinding Procedures

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists at the study site upon request.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The date and reason that the blind was broken must be recorded in the source documentation and CRF as applicable. The Investigator is to document and

report the action to the appropriate representative, without revealing the treatment given to the patient.

The designated safety representative retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the study drug and that potentially require expedited reporting to regulatory authorities.

H Data Handling and Record Keeping

H1 Confidentiality and Security

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. Largely, patient data will only be accessible to those with clearance. Efforts will be made to keep clinical information masked and protected through secure electronic passwords only available to those with clearance.

H2 Training

Before the first patient is entered into the study, a delegate from the study team will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and train them in any study specific procedures and system(s) utilized. Training will be conducted via Skype, Zoom, or another telecommunications application.

The PI will ensure that appropriate training relevant to the study is given to all study staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

H3 Case Report Forms and Source Documents

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

H4 Records Retention

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period or transferred to another location or party without written notification from authorized parties.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

During the study, a research representative is on site and will be available to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, and that study drug accountability checks are being performed

The study site will maintain detailed drug accountability logs, including the quantity of study drug received, dispensed, returned, and destroyed at the specified visit times. Any discrepancies in drug accountability will be documented and reported to the IRB as required. At the end of the study or upon participant withdrawal, any unused study drug will be collected and destroyed in accordance with local regulations and requirements.

I2 Auditing and Inspecting

Authorized representatives of a regulatory authority or an IRB/IEC may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, and any applicable regulatory requirements.

J Study Administration

J1 Funding Source and Conflicts of Interest

The funding source will come from the AMD/Retinal Disease Research Fund which has been awarded to principal investigator Dr. Rajendra Apte. There are no conflicts of interest for team members of this study relating to the experimental drug.

K References

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