Official Study Title: A Phase 2, Double-Masked, Randomized, Placebo-Controlled, Dose-Response Study Assessing the Safety and Efficacy of QA102 in Subjects with Dry Age-Related Macular Degeneration (AMD) (AMEND Study)

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A PHASE 2, DOUBLE-MASKED, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY ASSESSING THE SAFETY AND EFFICACY OF QA102 IN SUBJECTS WITH DRY AGE-RELATED MACULAR DEGENERATION (AMD)

(AMEND STUDY)

PROTOCOL QA102-CS201
VERSION 4.0, [redacted]

SPONSOR'S APPROVAL

The protocol has been approved by Smilebiotek Zhuhai Limited

Sponsor's Authorized Officer:

[redacted] Date

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1. SYNOPSIS

Sponsor/Company: Smilebiotek Zhuhai Limited [redacted]	**Medical Monitor:** [redacted]
Name of Investigational Product (IP): QA102 Oral Capsules	
Title of Study: A Phase 2, Double-Masked, Randomized, Placebo-Controlled, Dose-Response Study Assessing the Safety and Efficacy of QA102 in Subjects with Dry Age-Related Macular Degeneration (AMD) (AMEND Study)	
Study Centers: This is a multicenter study using approximately 30 sites in the United States.	
Treatment Period: 15 months	**Phase of Development:** 2

Primary Objective

- To evaluate the efficacy of QA102 oral capsules on the development of soft drusen, visual acuity (VA), and geographic atrophy (GA) or choroidal neovascularization (CNV) or the progression of GA in subjects with intermediate to advanced dry AMD.

Secondary Objective

- To evaluate the ocular and systemic safety of 2 dose levels of QA102 oral capsules.

Primary Endpoint

- In the study eye at Month 12, change from baseline in soft drusen volume (mm^3) as measured by spectral domain optical coherence tomography (SD-OCT).

Key Secondary Endpoints

- In the study eye at Month 12, change from baseline in best-corrected visual acuity (BCVA) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS).
- In the study eye at Month 12, change from baseline in low-luminance visual acuity (LLVA) as measured by ETDRS.

Other Secondary Endpoints

In the Study Eye and/or Fellow Eye

- Change from baseline in drusen volume (mm^3) as measured by SD-OCT at time points other than Month 12 (study eye) or at all time points (fellow eye).
- Change from baseline in BCVA as measured by ETDRS at time points other than Month 12 (study eye) or at all time points (fellow eye).
- Change from baseline in LLVA as measured by ETDRS at time points other than Month 12 (study eye) or at all time points (fellow eye).
- Change from baseline in GA area as measured by fundus autofluorescence (FAF) and/or SD-OCT.
- Change from baseline in GA area as measured by the square root transformation of area on FAF and/or SD-OCT.
- [redacted]
- [redacted]

- In the study eye at Month 15, proportion of subjects with disease progression, defined as (a) development of CNV, as assessed by SD-OCT and/or FAF, or (b) GA change from baseline of [redacted], as assessed by FAF. Both assessments will be conducted by the central reading center (CRC).
- Proportion of subjects with progression of GA, defined as a change from baseline of [redacted], at time points other than Month 15 (study eye) or at all time points (fellow eye), as determined by the CRC using FAF and/or SD-OCT.
- Proportion of subjects requiring rescue injections of anti-vascular endothelial growth factor (VEGF) therapies for CNV.
- [redacted]

Only in the Fellow Eye

- [redacted]

Study Design

This is a phase 2 double-masked, randomized, multi-center, placebo-controlled, dose-response study of QA102 oral capsules at 2 dose levels to evaluate the safety, tolerability, and efficacy of oral QA102 in subjects with intermediate to advanced dry AMD.

The primary objective of the study is to evaluate the efficacy of QA102 oral capsules on the development of soft drusen, VA, and GA or CNV or the progression of GA.

Approximately 30 sites will randomize a total of approximately 150 subjects to 1 of 3 treatment groups in a 1:1:1 ratio (50 subjects per group). Treatment randomization will be stratified according to baseline GA status (naïve versus non-naïve) in the study eye. Subjects are considered GA naïve if they have no evidence of GA in the study eye at baseline, as confirmed by the CRC. Every attempt will be made to enroll at least 30% (approximately 45 subjects) of the total subjects for each stratum. Each subject will receive either QA102 200 mg twice daily (BID), QA102 400 mg BID, or matching placebo BID for up to 15 months.

Clinic study visits will occur on Day -21 to Day -7 (screening); Day 1 (randomization); Day 7; Months 1, 2, and 3 (all ± 3 days); and Months 6, 9, 12, and 15 (all ± 7 days). In months when no clinic visit is scheduled (i.e., Months 4, 5, 7, 8, etc.), sites will contact each subject by telephone to update adverse events (AEs) and review concomitant medications (CMs).

Number of Subjects (Planned)

Approximately 150 subjects will be randomized.

Criteria for Inclusion

Subjects must meet all of the following criteria at screening (Visit 1) to be eligible for participation in this study:

1. Subject must be able to understand and willing to sign a written informed consent form (ICF) prior to the initiation of any study-specific procedures.
2. Subject must be age ≥50 years at the time of informed consent.
3. Subject must be able to take oral medications and willing to record daily adherence to taking their assigned capsules.
4. Subject must have adequate hematologic function as indicated by:
    - Platelet count ≥100 x 10^9/L

      Note: Use of transfusions or thrombopoietic agents to achieve screening platelet count criterion is prohibited.
    - Absolute neutrophil count (ANC) ≥1.0 x 10^9/L

      Note: Use of growth factors to maintain ANC criterion is not permitted.
    - Hemoglobin ≥9.0 g/dL

5. Subject must have adequate hepatic function as defined below:
    - Serum alanine aminotransaminase (ALT)/aspartate aminotransaminase (AST) ≤3 x upper limit of normal (ULN).
    - Serum bilirubin – total ≤1.5x ULN (unless due to Gilbert's syndrome or hemolysis, in which case total ≤3.0 x ULN).
6. Subject must have adequate renal function, defined as serum creatinine <2.0 mg/dL **or** estimated creatinine clearance ≥45 mL/min calculated by the Cockcroft-Gault (1976) formula using actual body weight.
7. Subject must have adequate coagulation profile as defined below:
    - Prothrombin time and activated partial thromboplastin time ≤1.5 x ULN for subjects who are not anticoagulated.
    - If the subject is anticoagulated, must have been on a stable dose of anticoagulant for ≥30 days prior to screening.
8. Female subjects must be:
    - Women of non-childbearing potential (WONCBP), or
    - Women of childbearing potential (WOCBP) with a negative pregnancy test at screening who agree to use protocol-defined methods of contraception for the duration of the study until 3 months after the last dose.
9. Males with female partners of childbearing potential must agree to use condoms (unless they are vasectomized) and their female partner should use protocol-defined methods of contraception for the duration of the study until 3 months after the last dose. Alternatively, male subjects must agree to abstain from sexual intercourse with WOCBP if this is their usual and preferred lifestyle. In addition, male subjects must agree to refrain from donating sperm for the duration of the study until 3 months after the last dose.
10. Subject must be willing and able to comply with study procedures and examinations.
11. In both eyes, subject must have visualizable retina, clear ocular media, and adequate pupillary dilation to ensure high-quality fundus imaging.

Specific to Study Eye

12. Subject must have one of the following:
    - extensive [redacted] intermediate-size drusen, or at least 1 large [redacted] drusen, to be confirmed by the CRC, or
    - GA (not involving the foveal center point) secondary to AMD, with the aggregate size of total GA(s) [redacted], to be confirmed by the CRC.

    Note: No more than approximately 70% of subjects will be enrolled in either group.
13. Subject must be able to correctly identify ≥35 ETDRS letters (approximately 20/200 Snellen equivalent).

Specific to Fellow Eye

14. Subject must have a diagnosis of advanced AMD (evidence of GA and/or CNV), to be confirmed by the CRC.

    Note: If both eyes have GA that meets the eligibility requirements, the eye with larger GA will be designated the study eye. If the GA sizes are equivalent, the eye with better VA will be designated the study eye. In the case of equal GA and VA across eyes, the right eye will be designated the study eye.

Criteria for Exclusion

Subjects who meet any of the following criteria at screening (Visit 1), unless otherwise noted, will be excluded from participation in this study.

1. Subject has ever received gene therapy (for any condition).
2. Subject is not capable of maintaining stable fixation for SD-OCT imaging.

3. Subject has blood pressure >180/110 (systolic above 180 OR diastolic above 110).
4. Subject has a laboratory value (hematology, serum chemistry, or urinalysis) that, in the opinion of the Investigator, is clinically significant and renders the subject unsuitable for enrollment.
5. Subject received an *active* investigational drug within 6 weeks (or 5 half-lives of the active, whichever is longer) prior to screening for this QA102 study. See also Exclusion 13.

   Note: Subjects with documented evidence of treatment with *placebo* ("sham-arm treatment") within 6 weeks of screening are eligible. Clinical trials solely involving observation or special diets are not exclusionary.
6. Subject is unwilling to stop intake of any vitamins for AMD (Age-Related Eye Disease Study [AREDS] vitamins or similar) for the duration of the study.
7. Subject has a clinically significant systemic disease (e.g., dementia, cancer and/or ongoing chemotherapy treatment, uncontrolled diabetes, myasthenia gravis, and/or any hepatic, renal, cardiovascular, or endocrine disorder, etc.) that might interfere with the study, in the judgment of the Investigator.
8. Subject has a medical or psychiatric condition(s) that, in the opinion of the Investigator, make consistent follow-up over the treatment period unlikely, or in general is a poor medical risk because of other systemic diseases or active uncontrolled infections.
9. Subject has a known infection or condition such as active hepatitis B virus, active hepatitis C virus, active or controlled human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS).
10. Subject has a recent or current history of drug or alcohol abuse, or participates in recreational drug use that, in the opinion of the Investigator, may limit the subject's ability to complete the protocol.
11. Subject received a live vaccine within 30 days prior to screening.
12. Subject had major surgery within 30 days prior to screening.

Specific to Study Eye

13. Subject has ever received, whether in an interventional trial or by prescription, a Food and Drug Administration (FDA)-approved treatment for GA. Use of such treatment during the QA102 study period also is prohibited.
14. [redacted]
15. Subject has GA or CNV due to causes other than AMD that developed between Visit 1 (screening) and Visit 2 (randomization).
16. Subject has endophthalmitis.
17. Subject has a hemorrhagic or serous pigment epithelial detachment (PED) within 500 µm of the foveal center point, to be confirmed by the CRC.
18. Subject has had retinal procedures or surgeries, or has a retinal pathology, such as a macular hole.
19. Subject has aphakia or absence of the posterior capsule.

Specific to Fellow Eye

20. [redacted]

In Either Eye

21. Subject has a visually significant cataract that, in the opinion of the Investigator, is likely to decrease VA by 3 lines or more during the study.
22. Subject had intraocular surgery with lens replacement within 3 months of screening.
23. Subject has any ophthalmic condition that could require surgery during the study period.
24. Subject has a concurrent ocular pathology that may contribute to vision loss (e.g., high myopes >-6.00 spherical equivalent [SE] prior to cataract surgery) or interfere with the acquisition of high-quality images.
25. Subject has an ocular condition that, in the opinion of the Investigator, might affect adequate imaging of the retina and/or or alter VA (e.g., herpetic ocular disease, vein occlusion, uveitis or other ocular

inflammatory disease, neovascular glaucoma, advanced cataract, optic neuropathy, diabetic retinopathy, cystoid macular edema, epiretinal membrane, vitreomacular traction, or corneal abnormalities, etc.).

26. Subject has intraocular pressure (IOP) >25 mmHg.
27. Subject requires more than 2 medications for management of IOP.

    Note: A combination medication counts as 2 medications.
28. Subject had a previous violation of the posterior capsule, unless it occurred because of yttrium aluminum garnet (YAG) laser posterior capsulotomy, at least 60 days prior to screening, in association with prior posterior chamber intraocular lens implantation.

Investigational Products, Dosage, and Mode of Administration

The active IP is supplied as oral dose capsules containing 200 mg of QA102. The reference IP (placebo) is supplied as matching oral dose capsules.

The assigned dose will be one of the following:

- One (1) 200 mg capsule and 1 placebo capsule BID = daily dose of 400 mg QA102
- Two (2) 200 mg capsules BID = daily dose of 800 mg QA102
- Two (2) placebo capsules BID = daily dose of 0 mg QA102

Both active and placebo capsules will be stored at [redacted]. Subjects will dose in the morning and evening, approximately 8-12 hours apart, taking the IP with water and with or without food.

Duration of Treatment

Each subject will receive either QA102 200 mg BID, QA102 400 mg BID, or matching placebo BID for up to 15 months.

Dose Interruptions or Discontinuation

Dosing may be interrupted for up to [redacted] to allow for resolution of treatment-emergent, treatment-related AEs with a severity of ≥Grade 2 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. If the treatment-emergent, treatment-related AE does not resolve or recover to Grade 1 within 14 days, IP administration will be permanently discontinued for that subject and the subject will be exited from the study. Multiple dose interruptions (including back-to-back interruptions) with AE resolution are allowed per the discretion of the Investigator, in consultation with the Medical Monitor, so long as total time off treatment (due to dose interruptions, treatment non-compliance, or a combination of the two) is [redacted].

IP administration also may be permanently discontinued for an individual subject upon the development of active CNV in the study eye, as confirmed by the CRC. The subject will be exited from the study.

Criteria for Evaluation

Efficacy:

- SD-OCT
- FAF
- BCVA
- LLVA
- Fundus photography

Safety:

- AE data
- Vital signs
- IOP (Goldmann applanation, iCare, or Tono-Pen)
- Electrocardiograms (ECGs)

- Slit lamp exam (SLE)
- Dilated fundus exam (DFE)
- Clinical laboratory tests

Statistical Considerations

Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of study medication.

Analysis Sets:

- The Safety (SAF) Analysis Set will include all randomized subjects who received any study medication. Subjects will be grouped by the actual treatment received.
- The Full Analysis Set (FAS) will include all randomized subjects who received any study medication and who provided a baseline BCVA measurement and at least 1 post-baseline BCVA measurement. Subjects will be grouped by randomized treatment.
- The Efficacy-Evaluable Analysis Set (EAS) will include all subjects in the FAS who completed 12 months of treatment or who discontinued earlier due to disease progression and had no major protocol deviations. Subjects will be grouped by randomized treatment.

Sample Size:

Approximately 150 subjects (50 per group) will be treated to obtain 120 evaluable subjects. A sample size of 120 evaluable subjects (40 per group) will provide approximately 80% power to detect [redacted] between the QA102 group and the placebo group. This assumes that the standard deviation of [redacted] and a one-sided test at the 5% level of significance. By combining two QA102 groups, this sample size will provide >90% power.

This sample size will also provide approximately 85% power to detect a difference of [redacted] in mean BCVA (or LLVA) between the QA102 groups and the placebo group. This assumes that the standard deviation of BCVA (or LLVA) is [redacted] and a one-sided test at the 5% level of significance.

Additionally, the sample size will provide approximately 85% power to detect [redacted] for the QA102 groups compared with the placebo group. This assumes that, in the absence of treatment, [redacted], the standard deviation of [redacted] change is [redacted], and a one-sided test at the 5% level of significance.

Hypotheses and Tests:

The study is designed to show the superiority of QA102 over placebo in terms of drusen volume, BCVA, and LLVA.

The hypothesis for the primary and key secondary endpoints is that at least 1 dose regimen of QA102 is superior to placebo with respect to the mean change from baseline in the study eye at Month 12. The hypotheses for each dose level of QA102 compared with placebo can be written as:

$$H_0: m_{QA,Post\text{-}dose} - m_{QABaseline} = m_{PL,Post\text{-}dose} - m_{PL,Baseline}$$

$$H_A: m_{QA,Post\text{-}dose} - m_{QA,Baseline} > m_{PL,\ Post\text{-}dose} - m_{PL,Baseline}$$

where m_{QA} and m_{PL} represent the mean values at baseline and post-dose visit for each dose level of QA102 and placebo, respectively.

Additionally, the hypothesis for each dose level of QA102 compared with placebo with respect to the mean rate of growth (slope) from baseline in square root area of GA lesion can be written as:

$$H_0: \beta_{QA} = \beta_{PL}$$
$$H_A: \beta_{QA} < \beta_{PL}$$

where β_{QA} and β_{PL} represent the mean rate of growth (slope) for each dose level of QA102 and placebo, respectively.

For the primary endpoint, the sequential testing procedure will be employed to control the overall Type I error rate at 5% with respect to multiple comparisons for the following hypotheses: 400 mg to placebo (H_1) and 200 mg to

placebo (H_2). The testing procedure will be done in a hierarchical order as H_1 and H_2. All other efficacy variables will be tested at the one-sided 0.05 level of significance.

Methodology:

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP).

Data will be summarized and tabulated using SAS® statistical analysis software. Descriptive statistics will be utilized for all safety and efficacy parameters. Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Safety data will be compared over time to assess change from baseline during treatment and follow-up. Dose-level differences will be assessed using appropriate parametric or non-parametric significance tests, as applicable. The analyses will be conducted for the study eye and for the fellow eye as deemed appropriate.

Interim Analysis:

An interim analysis will occur when roughly one-third of the total subjects are evaluable for the primary endpoint, change in drusen volume at Month 12. A futility monitoring of the change in drusen volume will be performed. The O'Brien-Fleming spending function is used to determine the futility test boundaries (Lan and DeMets 1983, O'Brien and Fleming 1979). The critical value for futility at interim is 0.494. The SAP will describe the planned interim analyses in greater detail.

The change in drusen volume, BCVA, and LLVA over time to Month 6 will be also evaluated.

The purposes of the interim analysis are to allow early stopping of the study for futility and to assess safety. An external, independent Data Review Committee (DRC) will review cumulative unmasked efficacy data and safety data and will have the responsibility to conduct a thorough safety assessment.

Efficacy Analysis:

Unless otherwise noted, summaries of efficacy will be presented by study eye for primary and key secondary endpoints, and by study eye and/or fellow eye for other secondary endpoints, as appropriate.

The analysis for the primary endpoint, change from baseline in drusen volume in the study eye at Month 12, will be based on a mixed-effects model for repeated measures (MMRM) to compare the treatment groups. The MMRM model will include baseline GA status (naïve versus non-naïve), treatment, time, and treatment by time interaction as fixed effects, and baseline as a covariate. Time ordering will be treated as a repeated measure within subjects, and an unstructured covariance matrix is assumed. If the model will not converge with the unstructured covariance structure, heterogeneous compound symmetry will be used instead. Furthermore, if the model fails to converge with heterogeneous compound symmetry, the heterogeneous Toeplitz (TOEPH) structure will be used. If the unstructured covariance structure is used, the denominator degrees of freedom will be computed using the Kenward-Roger (1997) method. The estimates of treatment effects will be provided along with corresponding two-sided 90% confidence intervals (CIs) and p-value. MMRM analysis does not require data imputation and uses only the observed data. The treatment effects estimated with MMRM are valid under the assumption of missingness at random (MAR). Any measurements after receipt of rescue therapy (anti-VEGF) will be considered as missing. To assess the robustness of the efficacy results, selected sensitivity analyses will be performed to assess the potential magnitude and direction of the impact of missing data.

Analyses for change from baseline in BCVA and LLVA in the study eye will proceed in the same manner as the analyses for the primary efficacy endpoint.

MMRM models also will be used to estimate the GA growth rate and its 90% CI. Mean rate of GA growth in mm^2/year and the mean rate of growth in mm/year from square root transformation of GA area in mm^2/year will be evaluated separately.

Similar analyses will be applied to other secondary endpoints with change from baseline measurements.

The frequency and percentage of subjects with disease progression in the study eye will be summarized and compared using the stratified Cochran-Mantel-Haenszel (CMH) test, controlling for baseline GA status (naïve versus non-naïve). A subject receiving any rescue (anti-VEGF) therapy during the study will be considered to have progression. Furthermore, the differences in proportions between the two treatment groups and two-sided 90%

exact CI will be estimated. In addition, time to progression will be assessed using the Cox proportional hazard (Cox PH) model that includes the main effects for treatment and baseline GA status (naïve versus non-naïve).

Safety Analysis:

All safety assessments, including AEs, vital sign measurements, IOP, ECGs, SLE, DFE, and CMs, will be tabulated and summarized where possible, using descriptive methodology, as needed, by time point. No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

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3. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransaminase
AMD	Age-related macular degeneration
ANC	Absolute neutrophil count
AREDS	Age-Related Eye Disease Study
AST	Aspartate aminotransaminase
β-hCG	Beta human chorionic gonadotropin
BCVA	Best-corrected visual acuity
BID	Twice daily
CFR	Code of Federal Regulations
CI	Confidence interval
CM	Concomitant medication
CMH	Cochran-Mantel-Haenszel test
CMP	Clinical Monitoring Plan
CNV	Choroidal neovascularization
Cox PH	Cox proportional hazard
CRA	Clinical Research Associate
CRC	Central reading center
CTCAE	Common Terminology Criteria for Adverse Events
DA	Disk area
DFE	Dilated fundus exam
DRC	Data Review Committee
EAS	Efficacy-Evaluable Analysis Set
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus autofluorescence
FAS	Full Analysis Set

Abbreviation	Definition
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
GA	Geographic atrophy
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational new drug
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
iRORA	Incomplete retinal pigment epithelium and outer retinal atrophy
IVT	Intravitreal
LLVA	Low-luminance visual acuity
MAR	Missing(ness) at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
MOP	Manual of Procedures
NCI	National Cancer Institute
PED	Pigment epithelial detachment
PI	Principal Investigator
PK	Pharmacokinetics
QA102	Octyl gallate
QC	Quality control
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD-OCT	Spectral domain optical coherence tomography
SE	Spherical equivalent
SLE	Slit lamp exam

Abbreviation	Definition
SOP	Standard operating procedures
SRF	Subretinal fluid
TCM	Traditional Chinese medicine
TEAE	Treatment-emergent adverse events
T_{max}	Time to maximum plasma concentration
TOEPH	Heterogeneous Toeplitz
ULN	Upper limit of normal
UPT	Urine pregnancy test
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
YAG	Yttrium aluminum garnet

4. INTRODUCTION

This study will be performed in accordance with regulatory requirements outlined in the US Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) E6 Guidelines.

4.1. Overview

Age-related macular degeneration (AMD) is a leading cause of irreversible visual dysfunction in individuals >50 years old (Friedman 2004). The pathogenesis of AMD is characterized by thickening of Bruch's membrane due to lipid and protein accumulation that leads to formation of subretinal pigment epithelial deposits that occur as discrete accumulations called drusen (Rickman 2013). Over time, the disease is characterized by atrophy of the retina with loss of vision.

There are 2 major types of AMD: dry (atrophic) and wet (neovascular or exudative). Most AMD starts as the dry type, and 10% to 20% of individuals with dry AMD progress to the wet type (Kwon 2017). For choroidal neovascularization (CNV), the hallmark of wet AMD, the standard therapy now includes intravitreal (IVT) injections of drugs that block vascular endothelial growth factor (VEGF).

Currently, other than the use of vitamin supplements and antioxidants in a subset of patients (Age-Related Eye Disease Study [AREDS] Research Group 2001), there is no effective prophylaxis or treatment to prevent the progression of dry AMD to either geographic atrophy (GA) or CNV. There are a number of investigational therapies for dry AMD, including complement-based therapeutics and anti-amyloid therapies (Holz 2018, Cabral de Guimaraes 2022), but most target existing GA rather than attempt to prevent its development. As of April 2023, one treatment for existing GA was FDA approved and another was under FDA review.

Using quantitative polymerase chain reaction methods, negative staining transmission electron microscopy, and high-throughput sequencing technologies, Wei (2018) found that resident microbiota inhabits the intraocular cavities in all eyes. A disease-specific signature of the microbial community differentiated several intraocular diseases, including AMD. Further, Wei (2018) found that an AMD-specific bacterium, *Bacillus megaterium*, induced activation of complement and retinal cell death *in vitro* and *in vivo*. These findings identified bacterial infection as a possible key pathogenic factor for dry AMD, and provide a novel direction for the diagnosis, treatment, and prevention of the disease.

Jin et al. (2018) conducted a randomized clinical study with IVT ranibizumab treatment with the addition of oral traditional Chinese medicine (TCM) in subjects with CNV. A total of 144 subjects with neovascular AMD received either IVT ranibizumab treatment as needed plus placebo or IVT ranibizumab treatment as needed plus TCM named ZQMT. Of note, ZQMT treatment resulted in numerical improvements in reducing retinal hemorrhage, fluid, and lesion size and the number of needed ranibizumab injections.

In an *in vitro* screening assay, Smilebiotek Zhuhai Limited identified a small molecule, QA102 [redacted], from the TCM composition. QA102 exhibited a strong inhibitory effect on *Bacillus megaterium*.

Smilebiotek Zhuhai Limited is developing QA102 as an oral treatment to slow the progression of early/intermediate to advanced (GA or CNV) stages in subjects with AMD. Note that the site of action for oral dosing is in the gastrointestinal system. However, QA102 is absorbed from the gastrointestinal system, and a low systemic exposure has been observed.

For further details regarding nonclinical studies, toxicology, pharmacokinetics (PK), and clinical experience, please refer to the Investigator's Brochure (IB).

4.2. Study Rationale

For patients at risk of developing GA, AREDS vitamins are a standard option, but they are classified as a dietary supplement and are of limited therapeutic value. The original AREDS study followed 3,640 subjects with early to late-stage AMD for a mean of 6.3 years. Data demonstrated that treatment with zinc alone or in combination with antioxidants might reduce the risk of progression to advanced AMD in a small subset of participants with Category 3 (extensive intermediate drusen, large drusen, or noncentral GA in 1 or both eyes) or Category 4 (advanced AMD or visual acuity [VA] <20/32 in 1 eye) degeneration. The risk of progression to advanced AMD was reduced by 25% for subjects taking antioxidants plus zinc (AREDS Research Group 2001). A subsequent study enrolled 4,203 subjects with intermediate to advanced AMD, followed for a mean of 5 years, to evaluate the additions of lutein and zeaxanthin and removal of beta-carotene from the original AREDS formulation. The adjusted formulation did not further reduce risk of progression to advanced AMD, but lutein and zeaxanthin were found to be an appropriate carotenoid substitute (AREDS2 Research Group 2013).

In clinical trials, IVT injection therapy for GA secondary to AMD has been associated with increased rates of wet AMD and episodes of intraocular inflammation (Apellis 2023, prescribing information). Subjects who convert to wet AMD are likely to be treated with anti-VEGF injections, which have been associated with the following adverse events (AEs): endophthalmitis; retinal detachment; ocular hypertension, hemorrhage, and/or inflammation; and systemic AEs (Falavarjani 2013).

Therapy that may slow the conversion of dry to wet AMD, particularly an intervention that avoids the complications of IVT injections, could be of value to subjects at risk of developing GA or CNV. A novel approach based on control of an AMD-specific bacterium (*Bacillus megaterium*), achieved through oral dosing of the QA102 molecule, is worthy of investigation.

4.3. Dose and Dose Frequency Rationale

The phase 1 study QA102-CS101 evaluated the safety and tolerability of single and multiple ascending oral doses of QA102 in healthy young adult subjects (age 18-59 years) and healthy older subjects (age 60-75 years). A single dose in the range of [redacted] and multiple doses of [redacted] mg twice daily (BID) and [redacted] BID for 4.5 days were safe and well tolerated in healthy young adult subjects.

When healthy older adult subjects were dosed with [redacted] BID for 4.5 days, 5 of 6 subjects (83.3%) reported a total of 8 treatment-emergent adverse events (TEAEs); all occurred within the [redacted] dose group. Of the 8 TEAEs, 7 were mild and considered by the Investigator to be related to study treatment. The most common TEAE was [redacted], reported by 4 subjects; [redacted] were reported by 1 subject each. The

remaining TEAE was moderate but not considered by the Investigator to be related to the investigational product (IP).

Based on the AE profile observed at 800 mg BID in older subjects, 400 mg BID was chosen as the highest dose for this phase 2 study to ensure the safety of study subjects.

The BID dosing frequency was chosen to exert a longer duration of pharmacological effect. The site of action for oral dosing is the gastrointestinal system, and QA102 traverses the gut rapidly based on human PK data from the QA102-CS101 study. Median time to maximum plasma concentration (T_{max}) was [redacted]. Mean oral clearance was high in all dose cohorts, and [redacted]. Exposure was overall dose-proportional in the dose range of 100 mg to 1,600 mg. Following BID administration of 200 mg or 800 mg QA102 for 4.5 days, there was no significant accumulation based on limited available data.

4.4. Benefit-Risk Assessment

Subjects with dry AMD may receive benefit (beyond an assessment of their medical status) from participating in this study, including the potential for slowed progression of AMD.

The risks of participation are primarily those associated with adverse reactions to the IP, although there may also be some discomfort from collection of blood samples and other study procedures. Because mild loose stool was observed in a subset of older subjects dosed with 800 mg QA102 BID, the highest dose in this phase 2 study has been reduced to 400 mg BID.

More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with QA102 may be found in the IB.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of QA102 oral capsules on the development of soft drusen, visual acuity (VA), and GA or CNV or the progression of GA in subjects with intermediate to advanced dry AMD.

5.2. Secondary Objective

The secondary objective of this study is to evaluate the ocular and systemic safety of 2 dose levels of QA102 oral capsules.

5.3. Primary Endpoint

In the study eye at Month 12, change from baseline in soft drusen volume (mm^3) as measured by spectral domain optical coherence tomography (SD-OCT).

5.4. Secondary Endpoints

Key Secondary Endpoints

- In the study eye at Month 12, change from baseline in best-corrected visual acuity (BCVA) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS).
- In the study eye at Month 12, change from baseline in low-luminance visual acuity (LLVA) as measured by ETDRS.

Other Secondary Endpoints

In the Study Eye and/or Fellow Eye

- Change from baseline in drusen volume (mm^3) as measured by SD-OCT at time points other than Month 12 (study eye) or at all time points (fellow eye).
- Change from baseline in BCVA as measured by ETDRS at time points other than Month 12 (study eye) or at all time points (fellow eye).
- Change from baseline in LLVA as measured by ETDRS at time points other than Month 12 (study eye) or at all time points (fellow eye).
- Change from baseline in GA area as measured by fundus autofluorescence (FAF) and/or SD-OCT.
- Change from baseline in GA area as measured by the square root transformation of area on FAF and/or SD-OCT.
- In the study eye, the estimated mean rate of growth (slope) based on GA area measured by FAF at ≥3 time points.
- Area under the curve for BCVA letters read on the ETDRS chart over the 15-month treatment period.
- In the study eye at Month 15, proportion of subjects with disease progression, defined as (a) development of CNV, as assessed by SD-OCT and/or FAF, or (b) GA change from

baseline of [redacted], as assessed by FAF. Both assessments will be conducted by the central reading center (CRC).

- Proportion of subjects with progression of GA, defined as a change from baseline of [redacted] mm^2, at time points other than Month 15 (study eye) or at all time points (fellow eye), as determined by the CRC using FAF and/or SD-OCT.
- Proportion of subjects requiring rescue injections of anti-VEGF therapies for CNV.
- [redacted]

Only in the Fellow Eye

- [redacted]

6. STUDY DESIGN

6.1. Overview of Study Design

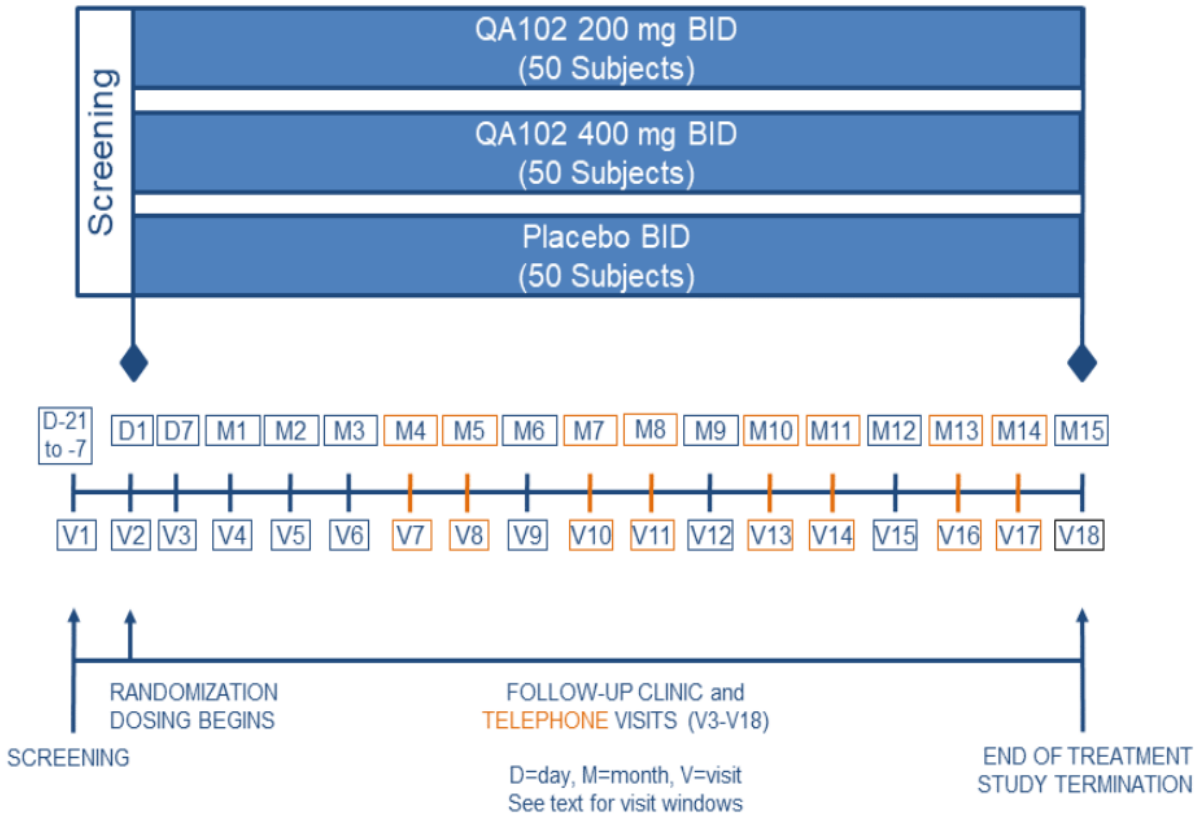
This is a phase 2 double-masked, randomized, multi-center, placebo-controlled, dose-response study of QA102 oral capsules at 2 dose levels to evaluate the safety, tolerability, and efficacy of oral QA102 in subjects with intermediate to advanced dry AMD.

The primary objective of the study is to evaluate the efficacy of QA102 oral capsules on the development of soft drusen, VA, and GA or CNV in high-risk eyes. High-risk eyes are defined by the Inclusion criteria (Section 7.1) specific to the study eye and fellow eye.

Approximately 30 sites will randomize a total of approximately 150 subjects to 1 of 3 treatment groups in a 1:1:1 ratio (50 subjects per group). Treatment randomization will be stratified according to baseline GA status (naïve versus non-naïve) in the study eye. Subjects are considered GA naïve if they have no evidence of GA in the study eye at baseline, as confirmed by the CRC. Every attempt will be made to enroll at least 30% (approximately 45 subjects) of the total subjects for each stratum. Each subject will receive either QA102 200 mg BID, QA102 400 mg BID, or matching placebo BID for up to 15 months.

Clinic study visits (Figure 1) will occur on Day -21 to Day -7 (screening); Day 1 (randomization); Day 7; Months 1, 2, and 3 (all ± 3 days); and Months 6, 9, 12, and 15 (all ± 7 days). In months when no clinic visit is scheduled (i.e., Months 4, 5, 7, 8, etc.), sites will contact each subject by telephone to update AEs and review concomitant medications (CMs). The Schedule of Assessments and Procedures is provided in Appendix 1.

Figure 1: Study Timeline



6.2. End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Assessments and Procedures (Appendix 1). The end of the study is defined as completion of the last visit or procedure shown in the schedule in the study.

7. STUDY ENROLLMENT AND WITHDRAWAL

7.1. Subject Inclusion Criteria

Subjects must meet all of the following criteria at screening (Visit 1) to be eligible for participation in this study:

1. Subject must be able to understand and willing to sign a written informed consent form (ICF) prior to the initiation of any study-specific procedures.
2. Subject must be age ≥50 years at the time of informed consent.
3. Subject must be able to take oral medications and willing to record daily adherence to taking their assigned capsules.
4. Subject must have adequate hematologic function as indicated by:
   - Platelet count ≥100 x 10^9/L

   Note: Use of transfusions or thrombopoietic agents to achieve screening platelet count criterion is prohibited.

   - Absolute neutrophil count (ANC) ≥1.0 x 10^9/L

   Note: Use of growth factors to maintain ANC criterion is not permitted.

   - Hemoglobin ≥9.0 g/dL
5. Subject must have adequate hepatic function as defined below:
   - Serum alanine aminotransaminase (ALT)/aspartate aminotransaminase (AST) ≤3 x upper limit of normal (ULN).
   - Serum bilirubin – total ≤1.5x ULN (unless due to Gilbert's syndrome or hemolysis, in which case total ≤3.0 x ULN).
6. Subject must have adequate renal function, defined as serum creatinine <2.0 mg/dL **or** estimated creatinine clearance ≥45 mL/min calculated by the Cockcroft-Gault (1976) formula using actual body weight.
7. Subject must have adequate coagulation profile as defined below:
   - Prothrombin time and activated partial thromboplastin time ≤1.5 x ULN for subjects who are not anticoagulated.
   - If the subject is anticoagulated, must have been on a stable dose of anticoagulant for ≥30 days prior to screening.
8. Female subjects must be:
   - Women of non-childbearing potential (WONCBP), or
   - Women of childbearing potential (WOCBP) with a negative pregnancy test at screening who agree to use protocol-defined methods of contraception for the duration of the study until 3 months after the last dose.
9. Males with female partners of childbearing potential must agree to use condoms (unless they are vasectomized) and their female partner should use protocol-defined methods of

contraception for the duration of the study until 3 months after the last dose. Alternatively, male subjects must agree to abstain from sexual intercourse with WOCBP if this is their usual and preferred lifestyle. In addition, male subjects must agree to refrain from donating sperm for the duration of the study until 3 months after the last dose.

10. Subject must be willing and able to comply with study procedures and examinations.
11. In both eyes, subject must have visualizable retina, clear ocular media, and adequate pupillary dilation to ensure high-quality fundus imaging.

Specific to Study Eye

12. Subject must have one of the following:
    - extensive [redacted] intermediate-size drusen, or at least 1 large [redacted] drusen, to be confirmed by the CRC, or
    - GA (not involving the foveal center point) secondary to AMD, with the aggregate size of total GA(s) [redacted] to be confirmed by the CRC.

    Note: No more than approximately 70% of subjects will be enrolled in either group.
13. Subject must be able to correctly identify ≥35 ETDRS letters (approximately 20/200 Snellen equivalent).

Specific to Fellow Eye

14. Subject must have a diagnosis of advanced AMD (evidence of GA and/or CNV), to be confirmed by the CRC.

    Note: If both eyes have GA that meets the eligibility requirements, the eye with larger GA will be designated the study eye. If the GA sizes are equivalent, the eye with better visual acuity (VA) will be designated the study eye. In the case of equal GA and VA across eyes, the right eye will be designated the study eye.

7.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria at screening (Visit 1), unless otherwise noted, will be excluded from participation in this study.

1. Subject has ever received gene therapy (for any condition).
2. Subject is not capable of maintaining stable fixation for SD-OCT imaging.
3. Subject has blood pressure >180/110 (systolic above 180 OR diastolic above 110).
4. Subject has a laboratory value (hematology, serum chemistry, or urinalysis) that, in the opinion of the Investigator, is clinically significant and renders the subject unsuitable for enrollment.
5. Subject received an *active* investigational drug within 6 weeks (or 5 half-lives of the active, whichever is longer) prior to screening for this QA102 study. See also Exclusion 13.

   Note: Subjects with documented evidence of treatment with *placebo* ("sham-arm treatment") within 6 weeks of screening are eligible. Clinical trials solely involving observation or special diets are not exclusionary.

6. Subject is unwilling to stop intake of any vitamins for AMD (AREDS vitamins or similar) for the duration of the study.
7. Subject has a clinically significant systemic disease (e.g., dementia, cancer and/or ongoing chemotherapy treatment, uncontrolled diabetes, myasthenia gravis, and/or any hepatic, renal, cardiovascular, or endocrine disorder, etc.) that might interfere with the study, in the judgment of the Investigator.
8. Subject has a medical or psychiatric condition(s) that, in the opinion of the Investigator, make consistent follow-up over the treatment period unlikely, or in general is a poor medical risk because of other systemic diseases or active uncontrolled infections.
9. Subject has a known infection or condition such as active hepatitis B virus, active hepatitis C virus, active or controlled human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS).
10. Subject has a recent or current history of drug or alcohol abuse, or participates in recreational drug use that, in the opinion of the Investigator, may limit the subject's ability to complete the protocol.
11. Subject received a live vaccine within 30 days prior to screening.
12. Subject had major surgery within 30 days prior to screening.

Specific to Study Eye

13. Subject has ever received, whether in an interventional trial or by prescription, an FDA-approved treatment for GA. Use of such treatment during the QA102 study period also is prohibited.
14. [redacted]
15. Subject has GA or CNV due to causes other than AMD that that developed between Visit 1 (screening) and Visit 2 (randomization).
16. Subject has endophthalmitis.
17. Subject has a hemorrhagic or serous pigment epithelial detachment (PED) within 500 µm of the foveal center point, to be confirmed by the CRC.
18. Subject has had retinal procedures or surgeries, or has a retinal pathology, such as a macular hole.
19. Subject has aphakia or absence of the posterior capsule.

Specific to Fellow Eye

20. Subject has monocular vision impairment, defined as having no light perception in the fellow eye with adequate vision in the study eye.

In Either Eye

21. Subject has a visually significant cataract that, in the opinion of the Investigator, is likely to decrease VA by 3 lines or more during the study.

22. Subject had intraocular surgery with lens replacement within 3 months of screening.
23. Subject has any ophthalmic condition that could require surgery during the study period.
24. Subject has a concurrent ocular pathology that may contribute to vision loss (e.g., high myopes >-6.00 spherical equivalent [SE] prior to cataract surgery) or interfere with the acquisition of high-quality images.
25. Subject has an ocular condition that, in the opinion of the Investigator, might affect adequate imaging of the retina and/or or alter VA (e.g., herpetic ocular disease, vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, advanced cataract, optic neuropathy, diabetic retinopathy, cystoid macular edema, epiretinal membrane, vitreomacular traction, or corneal abnormalities, etc.).
26. Subject has intraocular pressure (IOP) >25 mmHg.
27. Subject requires more than 2 medications for management of IOP.

    Note: A combination medication counts as 2 medications.
28. Subject had a previous violation of the posterior capsule, unless it occurred because of yttrium aluminum garnet (YAG) laser posterior capsulotomy, at least 60 days prior to screening, in association with prior posterior chamber intraocular lens implantation.

7.3. Subject Number and Identification

Subjects will be assigned a unique identification number at screening (Visit 1). The format will be XXXYYY, where XXX represents the site number and YYY the unique subject number.

7.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. Minimal information, including demography, screen failure details, eligibility criteria, and any serious adverse event (SAE), will be recorded.

Individuals who do not meet the criteria for participation in this trial (screen failure) at the completion of Visit 1 because of the following may be rescreened:

- Prohibited medications from which the subject may discontinue for purposes of screening eligibility (with approval from the Investigator based on clinical safety).
- Exclusionary medical history status at time of screening that will change (e.g., ocular infection, other transient medical condition, surgical history duration, etc.).
- Subject screen failed under a previous version of the protocol but may be eligible under the amended protocol.

Rescreened subjects will be assigned a new participant number.

7.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. An Investigator may discontinue or withdraw a subject from the study for the following reasons:

- Study terminated by the Sponsor
- Withdrawal of consent
- Lost to follow-up
- Pregnancy
- Significant study treatment/intervention non-compliance. Note: Subject must be exited from the study if IP non-compliance and/or dose interruptions cumulatively total ≥11 weeks off treatment (see also Section 7.7).
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject (see also Section 7.7)
- Disease progression that requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for subject discontinuation or withdrawal from the study will be recorded in the electronic case report form (eCRF). Subjects who sign the ICF and are randomized but do not receive the study intervention may be replaced.

Those who sign the ICF, are randomized, receive the study treatment/intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

In the event of subject discontinuation, the Investigator will make every attempt to have the subject complete Visit 18 (Month 15) assessments as soon as possible. The reason for premature discontinuation will be recorded in the subject chart and entered in the eCRF. Other procedures may be performed at the discretion of the Investigator (or designee) and/or Sponsor. The Investigator (or designee) may request that the subject return for an additional follow-up visit.

All subjects who withdraw due to an AE will be followed until resolution of the AE or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

7.6. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for a scheduled clinic visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return for a required clinic study visit:

- The site will attempt to contact the subject and reschedule the missed visit within 1 week, 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 (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will 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.

7.7. Subject Dose Interruption or Discontinuation

Dosing may be interrupted for up to [redacted] to allow for resolution of treatment-emergent, treatment-related AEs with a severity of ≥Grade 2 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (Section [redacted]

Prior to that threshold, if discontinuation of IP is deemed in the best interest of a subject, the Investigator should discuss the case with the Medical Monitor prior to exiting the subject from the study.

IP administration also may be permanently discontinued for an individual subject upon the development of active CNV in the study eye, as confirmed by the CRC. The subject will be exited from the study (see Section 8.5.1).

The Investigator should make every attempt to have the subject complete Visit 18 (Month 15, End of Study) assessments within 7 days (± 3 days) after the final dose of IP.

Subjects who develop an SAE or another AE meeting the discontinuation criteria will be carefully monitored, which may include the following at the discretion of the Investigator: additional clinical laboratory tests and/or other clinical investigations; additional visits or follow-up after the exit visit; specialist consultation.

8. STUDY TREATMENT

8.1. Investigational Products

Two IPs will be administered during this study: QA102 200 mg capsules and placebo capsules.

8.1.1. Description

Both active and reference IP are off-white, odorless capsules contained in standard medication bottles containing 30 capsules each (Table 1). Oral intake with water (with or without food) is the route of administration.

Table 1: Active and Reference IPs

	Active Investigational Product	**Placebo Control**
Product	QA102	Placebo
Chemical name	[redacted]	N/A
Dosage form	Capsule	Capsule
Unit dose	200 mg	N/A
Route of administration	Oral	Oral
Physical description	[redacted]	
Manufacturer		

8.1.2. Dosage and Administration

Active IP is supplied as oral dose capsules containing 200 mg of QA102. Reference IP (placebo) is supplied as matching oral dose capsules. [redacted]

[redacted]

The first dose will take place in clinic; all subsequent dosing will take place outside the clinic, BID for 15 months. Subjects will be instructed to dose in the morning and evening, with 8-12 hours between doses. Subjects are to take IP with water, and with or without food.

8.2. Preparation/Storage/Handling/Accountability

8.2.1. Packaging

IP will be supplied in conventional high-density polyethylene bottles containing 30 capsules each, sufficient for 15 days of dosing BID. [redacted]

Bottle labels will contain the following information: study reference code, bottle number including A or B designation, subject ID, coded lot number, contents, dosing instructions, storage temperature, required statement(s) per regulatory agency, and Sponsor.

Kit labels will contain the following information: study reference code, kit number, coded lot number, subject ID, contents, dosing instructions, storage temperature, required statement(s) per regulatory agency, and Sponsor.

8.2.2. Storage and Stability

At clinical sites, IP will be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide IP to any subject not participating in this study.

[redacted] Subjects will be instructed on the proper storage of IP.

8.2.3. Preparation

Neither QA102 nor placebo requires preparation by the Investigator or subject.

8.2.4. Accountability

Used and unused IP will be maintained at the site for accountability by the clinical study monitor. When authorized by the Sponsor and after the clinical study monitor has verified drug accountability is complete and accurate, all used and unused IP will be returned to the contracted drug vendor for final disposal.

8.3. Measures to Minimize Bias

To minimize bias, this study is randomized and double-masked.

Subjects will be randomized to treatment assignment. Treatment randomization will be stratified according to baseline GA status (naïve versus non-naïve). If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data.

A randomization schedule will be generated by the electronic data capture (EDC) system. The EDC will be used for randomization and unmasking.

[redacted]

[redacted]

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's Medical Monitor after consultation with the Sponsor.

8.4. Treatment Compliance

Masked capsules will be self-administered by the subject. Subjects are required to return all used and unused IP. The materials returned will provide primary evidence of compliance, with the daily dosing diary as secondary evidence, if needed.

If the returned IP shows and/or the subject reports more than 5% missed doses over any clinic visit interval, he or she will be carefully reinstructed on dosing and that education will be documented on the dispensation form and in the subject's eCRF.

8.5. Concomitant and Prohibited Medications

Any medication taken by a subject during the study and the reason for its use will be documented in the source data. No prescription or nonprescription medication is expressly prohibited during this study, with the exception of the following:

- AREDS (or similar) vitamins. Subjects should stop taking AREDS (or similar) vitamins after screening and throughout the 15-month study.
- In the study eye, FDA-approved treatment for GA. No prior or concurrent use is allowed.

Elective or required non-ocular surgery during the study period does not constitute a protocol deviation. Any interruption to IP should be documented in the source data.

8.5.1. Rescue Scenarios

The following actions will be taken for specific subject conditions related to the development or progression of GA or CNV or the occurrence of SAEs:

- If the study eye progresses to CNV, the subject will receive the care her/his physician thinks appropriate. The subject will be exited from the study.
- If the study eye progresses to GA, the subject will remain in the study and the size of GA will be monitored. No other treatment will be allowed for controlling GA, including AREDS (or similar) vitamins or any FDA-approved therapy for GA.
- If the fellow eye develops CNV, the subject will remain in the study. Local (intraocular) treatment, including anti-VEGF injections (ranibizumab, aflibercept, bevacizumab, faricimab-svoa), will be allowed for controlling CNV. No systemic treatments, including AREDS (or similar) vitamins, will be allowed.
- If the fellow eye develops GA, the subject will remain in the study. Local treatment with an FDA-approved GA therapy will be allowed. No systemic treatments, including AREDS (or similar) vitamins, will be allowed.

- If an SAE other than CNV or GA occurs in the study eye, the Investigator and Medical Monitor will confer to determine whether the subject should be exited from the study. If exited, the subject will receive the care her/his physician thinks appropriate.

9. STUDY PROCEDURES

Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all subjects prior to any study-related procedures being performed. The Schedule of Assessments and Procedures (Appendix 1) lists the procedures that should occur at each study visit. Ocular assessments should be performed in the order listed within each visit.

9.1. Visit 1 (Screening): Day -21 to Day -7

The following procedures will be performed on all subjects at the screening visit:

- Explain the purpose and conduct of the study to the subject, answer the subject's questions, and obtain written informed consent and HIPAA authorization.
- Obtain information including demographics, iris color, concomitant medications, ocular and systemic medical and medication history (prior 6 weeks), and surgical history.
- Determine study eligibility based on Inclusion/Exclusion criteria.
- Vital signs and body weight
- 12-lead safety electrocardiogram (ECG; must occur prior to blood sampling)
- Urine pregnancy test (UPT) for WOCBP or follicle-stimulating hormone (FSH) test for post-menopausal women <55 years of age
- Blood and urine samples for clinical labs: chemistry, hematology, coagulation, urinalysis
    - Although the subject must be seen for screening no later than Day -7, clinical lab results may be received as late as Day 1.
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- Slit lamp exam (SLE)
- Dilated fundus exam (DFE)
- Record AEs.

9.2. Visit 2 (Randomization): Day 1

The following procedures will be performed at the randomization visit:

- Update CMs.
- Record AEs.

- Confirm Visit 1 lab results and ocular assessments are consistent with Inclusion/Exclusion criteria and subject is eligible for randomization.
- Vital signs
- BCVA
- LLVA
- IOP
- SLE
- DFE
- FAF, SD-OCT, and fundus photography **only if** the onset of CNV is suspected, based on a significant decrease in VA (loss of ≥15 ETDRS letters) from Visit 1 to Visit 2. In this case, randomization and IP dispensation will be delayed until the CRC reviews the Visit 2 photos and FAF and SD-OCT data. If the CRC does *not* confirm CNV, the subject will return to the site for randomization and IP dispensation (no repeat assessments) as soon as possible. The date of the return visit will count as Day 1.
- Trained site staff will conduct the following procedures after completion of the assessments listed above.
    - Enter subject information in the EDC to determine randomization code and kit numbers.

[redacted]

    - Per the IP Guidance Manual, dispense an official study tote bag containing IP kits (sufficient to dose until Visit 4).
    - Issue dosing diary and train subject in diary completion. Instruct the subject to bring the dosing diary and all used and unused IP kits to every clinic visit.

[redacted]

9.3. Visit 3: Day 7

The following procedures will be performed at Visit 3:

- Update CMs.
- Record AEs.
- Vital signs
- BCVA
- LLVA
- IOP
- SLE
- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance. Return materials to the subject.

9.4. Visit 4: Month 1 (Week 4) ± 3 days

The following procedures will be performed at Visit 4:

- Update CMs.
- Record AEs.
- Vital signs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE
- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.
- Dispense new IP kits and dosing diary.

9.5. Visit 5: Month 2 (Week 8) ± 3 days

The following procedures will be performed at Visit 5:

- Update CMs.
- Record AEs.
- Vital signs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE
- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.
- Dispense new IP kits and dosing diary.

9.6. Visit 6: Month 3 (Week 13) ± 3 days

The following procedures will be performed at Visit 6:

- Update CMs.
- Record AEs.
- Vital signs
- Blood and urine samples for clinical labs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE
- DFE

- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.
- Dispense new IP kits and dosing diary.

9.7. Telephone Visits (all ± 7 days)

Visit 7 (Month 4/Week 17)
Visit 8 (Month 5/Week 21)
Visit 10 (Month 7/Week 30)
Visit 11 (Month 8/Week 34)
Visit 13 (Month 10/Week 43)
Visit 14 (Month 11/Week 47)
Visit 16 (Month 13/Week 56)
Visit 17 (Month 14/Week 60)

At telephone visits, the following procedures will be performed:

- Update CMs.
- Record AEs.
- Remind subject to dose as instructed and record dosing information in the daily diary. If the subject self-reports compliance issues, offer retraining by phone.

9.8. Visit 9: Month 6 (Week 26) ± 7 days

The following procedures will be performed at Visit 9:

- Update CMs.
- Record AEs.
- Vital signs
- UPT for WOCBP
- Blood and urine samples for clinical labs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE
- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.
- Dispense new IP kits and dosing diary.

9.9. Visit 12: Month 9 (Week 39) ± 7 days

The following procedures will be performed at Visit 12:

- Update CMs.
- Record AEs.
- Vital signs
- Blood and urine samples for clinical labs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE
- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.
- Dispense new IP kits and dosing diary.

9.10. Visit 15: Month 12 (Week 52) ± 7 days

The following procedures will be performed at Visit 15:

- Update CMs.
- Record AEs.
- Vital signs
- UPT for WOCBP
- Blood and urine samples for clinical labs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE

- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.
- Dispense new IP kits and dosing diary.

9.11. Visit 18 (End of Study/Early Termination): Month 15 (Week 65) ± 7 days

The following procedures will be performed at Visit 18 or in the event of early subject discontinuation:

- Update CMs.
- Record AEs.
- Vital signs
- 12-lead safety ECG (must occur prior to blood sampling)
- UPT for WOCBP
- Blood and urine samples for clinical labs
- BCVA
- LLVA
- IOP
- SD-OCT
- FAF
- Fundus photography
- SLE
- DFE
- Per the IP Guidance Manual, collect and review IP kits and dosing diary to assess compliance.

9.12. Unscheduled Visits

The Investigator or site staff may arrange for an unscheduled visit to dispense IP or to follow AEs as needed.

10. STUDY ASSESSMENTS

The Schedule of Assessments and Procedures (Appendix 1) provides a list of study assessments and evaluations to be performed and the timing of each.

10.1. Efficacy Evaluations

The primary evaluation of efficacy is the change from baseline in soft drusen volume (mm^3) in the study eye at Month 12, as measured by SD-OCT. The key secondary evaluations of efficacy are the change from baseline in BCVA and LLVA in the study eye at Month 12, as measured by ETDRS. Additional measures of efficacy make use of FAF and fundus photography.

10.1.1. Fundus Autofluorescence

FAF is a non-invasive imaging technique that detects fluorophores, naturally occurring molecules that absorb and emit light of specified wavelengths. Certification of the equipment and examiners at each clinical trial site will occur prior to evaluation of study subjects. At screening (Visit 1), retinal images will be submitted to the CRC for determination of eligibility. For detailed instructions on fundus autofluorescence testing, image capture specifications and approved instruments, please refer to the Manual of Procedures (MOP).

10.1.2. Spectral Domain Optical Coherence Tomography

SD-OCT has been developed for non-invasive cross-sectional imaging in biological systems. SD-OCT uses low-coherence interferometry to produce a two-dimensional image of optical scattering from internal tissue microstructures in a way that is analogous to ultrasonic pulse-echo imaging. SD-OCT has longitudinal and lateral spatial resolutions of a few micrometers and can detect reflected signals as small as ~10^{-10} of the incident optical power. For detailed instructions, please refer to the MOP.

10.1.3. Best-Corrected Visual Acuity and Low-Luminance Visual Acuity

BCVA and LLVA will be obtained through subjective manifest refraction and measured by a physician or a trained professional, separately for the study eye and fellow eye at each visit. Manifest refraction, BCVA, and LLVA will be obtained prior to all other procedures that require contact with the eye or instillation of any eye drops. Subjects' pupils will not be dilated at the time of VA testing at any study visit. Subjects wearing contact lens will be asked to remove their lenses 30 minutes prior to VA testing. All vision examinations will be performed by study-certified examiners in a certified lane.

10.1.4. Fundus Photography

Fundus photography is the process of taking serial photographs of the interior of the eye through the pupil. A fundus camera is a specialized low-power microscope attached to a camera used to examine structures such as the optic disc, retina, and lens. Fundus photography is primarily used to document and allow scrutiny of the ocular fundus, relying on the discernment of disease pathology by an experienced specialist who interprets the images, similar to the interpretation of a fundus examination performed during ophthalmoscopy. Although not yet routinely used, automated image analysis methods to detect abnormalities in retinal images have also been developed (Abràmoff et al. 2010). For more information, refer to the MOP.

10.2. Safety Evaluations

The safety of QA102 will be evaluated through routine assessments conducted regularly throughout the subject's treatment period, as outlined in Appendix 1 and described below.

10.2.1. Vital Signs

Vital signs assessments will include body temperature, respiratory rate, pulse rate, pulse oximetry, and systolic and diastolic blood pressure while the subject is in a supine or seated position and before any blood draws. Blood pressure and pulse rate will be collected after the subject has rested in a quiet setting without distractions (e.g., television, mobile phones) for at least 5 minutes. It is recommended that blood pressure be obtained using the same arm and the same type of equipment for each assessment.

Abnormal vital signs results should be repeated after 5 minutes; the results of both measurements will be recorded in the eCRF.

Any clinically significant change in vital signs, as determined by the Investigator, that occurs after the ICF is signed will be reported as an AE.

10.2.2. Intraocular Pressure (Goldmann Applanation, iCare, or Tono-Pen)

Contact tonometry is performed to determine IOP. The same method should be used for all visits at which IOP is measured. For more information, refer to the MOP.

10.2.3. Electrocardiogram

All subjects will undergo a 12-lead safety ECG at screening (Visit 1) and Month 15 (Visit 18) (or at early termination). The ECG is to be performed with the subject having rested for at least 5 minutes before each reading. The ECG must be performed prior to blood sampling.

Any clinically significant change in the ECG, as determined by the Investigator, that occurs after the ICF is signed will be reported as an AE.

10.2.4. Slit Lamp Exam

Ocular signs will be assessed by the Investigator using a slit lamp per standard clinical practice. The same examiner should conduct all SLEs at each visit for a given subject throughout the study.

The Investigator must examine the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil, and the lens of each eye for evidence of erythema and/or edema, opacities or other signs of abnormalities and record a grading for each tissue/structure, as specified in the MOP. Observations will be documented in the eCRF.

10.2.5. Dilated Fundus Exam

Binocular indirect ophthalmoscopy will be performed for each eye, with pupil dilation, at each clinic visit. Areas to be assessed include cup-to-disc ratio, retina, macula, choroid, and vitreous, as detailed in the MOP. A description of any clinically significant abnormalities will be documented in the eCRF.

10.2.6. Clinical Laboratory Assessments

All clinical laboratory testing (e.g., chemistry, hematology, coagulation, and urinalysis) will be performed using established methods. Abnormal laboratory values that are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved.

Any clinically significant change in lab values, as determined by the Investigator, that occurs after the ICF is signed will be reported as an AE.

Blood samples for laboratory assessments will be collected by a trained staff member designated and/or approved by the Investigator. Details for the collection, processing, storage, and shipment of samples for laboratory safety determinations will be provided in the Laboratory Manual.

10.2.6.1. Hematology and Coagulation

The hematology and coagulation parameters to be studied are provided in Table 2. Additional details are available in the Laboratory Manual.

Table 2: Hematology and Coagulation Laboratory Parameters

Hematology	Coagulation
Erythrocytes	Activated partial thromboplastin time
Hematocrit	Prothrombin time (seconds)
Hemoglobin	Prothrombin time (International Normalized Ratio)
Platelet count	
White blood cell count	
White blood cell differential and absolute cell counts:	
Basophils	
Eosinophils	
Lymphocytes	
Monocytes	
Neutrophils	

10.2.6.2. Blood Chemistry

The blood chemistry parameters to be studied are provided in Table 3. Additional details are available in the Laboratory Manual.

Table 3: Blood Chemistry Parameters

Chemistry	Other
Alanine aminotransaminase Albumin Alkaline phosphatase Amylase Aspartate aminotransaminase Bicarbonate Blood urea nitrogen Calcium Chloride Creatine kinase Creatinine Gamma-glutamyl transferase Glucose (fasting or non-fasting) Inorganic phosphorous Lactate dehydrogenase Lipase Magnesium Potassium Sodium Total bilirubin (direct and indirect)* Total protein Uric acid	Others, if indicated by emerging data

* Assessment of subtypes is required only if total bilirubin is abnormal.

10.2.6.3. Urinalysis

The urinalysis parameters to be studied are provided in Table 4. Additional details are available in the Laboratory Manual.

Table 4: Urinalysis Parameters

Urinalysis (Dipstick may be used)	Urinalysis Microscopic (Sedimentation)
Blood Glucose Ketones Protein Potential hydrogen (pH) Specific gravity	Red blood cell count White blood cell count Casts

10.2.6.4. Pregnancy

Subjects who become pregnant during the study should not receive further study drug and should be followed according to the procedures outlined in Section 10.4.2.

A urine beta human chorionic gonadotropin (β-hCG) test for WOCBP will be performed at screening (Visit 1) and Months 6, 12, and 15 (Visits 9, 15, and 18, respectively). The definitions of women of childbearing potential and women of non-childbearing potential are provided in Appendix 3.

Serum FSH levels will be assessed at screening only in post-menopausal females.

10.3. Adverse Events and Serious Adverse Events

AEs will be monitored throughout the study. Subjects will be encouraged to report any adverse findings during the study whether or not they are related to IP. These can be collected either in an unsolicited fashion without any prompting or in response to a general question such as: "Have you noticed any difference in your overall health status since the last visit?" (or, at screening, "since signing the ICF").

All AEs will be captured in the appropriate eCRF. Information to be collected at minimum includes event description, onset, assessment of severity, relationship to the IP, and outcome.

The Investigator will record all AEs with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for serious AEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the subject is screened will be considered as medical history and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

An AE is treatment-emergent if the onset time is after administration of IP through the final study visit.

10.3.1. Definitions

10.3.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

An AE or suspected adverse reaction is considered "serious" if, in the view of the Investigator, Medical Monitor, or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (Note: "Life-threatening" refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.)

Inpatient hospitalization or prolongation of existing hospitalization (Note: AEs requiring hospital admissions that are less than 24 hours in duration do not meet this criterion. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups, and for which the timing of the hospitalization is not changed due to worsening of condition warranting the procedure, do not meet this criterion.)

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect

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

10.3.1.2. Overdose and Medication Errors

Overdoses and medication errors will be collected as part of study drug dosing information and/or as a protocol violation, as required.

- Overdose: The administration of a quantity of IP, given per administration or cumulative, that is above the instructed dose according to the protocol.
- Medication error: An unintentional error in dispensing or administration of IP not in accordance with the protocol.

10.3.2. Classification of Adverse Events

10.3.2.1. Severity of Adverse Events

The Investigator will provide a severity grade for each AE according to the CTCAE, version 5.0. Toxicities that are not specified in the CTCAE will be defined as follows:

- Grade 1 (Mild): Transient or mild discomfort (<48 hours); no medical intervention/ therapy required.
- Grade 2 (Moderate): Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- Grade 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
- Grade 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospice or hospital care probable.
- Grade 5: Death.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as “serious,” which is a regulatory term defined by specific criteria (refer to Section 10.3.1.1).

For all AEs that require subject withdrawal from the study, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Follow-up laboratory results should be filed with the subject's source documentation.

10.3.2.2. Relationship of Adverse Events

All AEs must have their relationship to study intervention assessed by the Investigator, who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the IP must always be suspect.

- **Unrelated:** No reasonable possibility that the administration of the IP caused the event, no temporal relationship between the IP and event onset, or an alternate etiology has been established.
- **Related:** Is known to occur with the IP, is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, then the AE should be considered "related."

10.3.2.3. Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the IP, but are not specifically mentioned as occurring with the particular IP under investigation.

The Investigator will be responsible for determining whether an AE is unexpected (i.e., if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP).

10.3.3. Specific Instructions for Recording Adverse Events in the eCRF

10.3.3.1. Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of an AE, the diagnosis should be recorded in the eCRF rather than the individual signs and symptoms (e.g., record only hepatitis rather than elevated transaminases, bilirubin, jaundice); however, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE in the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up and should replace the individual signs and/or symptoms as the event in the eCRF.

10.3.3.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the AE in the eCRF or record the primary cause in the AE as well (e.g., dehydration due to severe vomiting). However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events in the eCRF. For example, if severe vomiting leads to acute renal failure, both events should be recorded in the eCRF.

10.3.3.3. Persistent and Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution or change in severity, between subject evaluation time points. Such events should only be recorded once on the AE eCRF page. If a persistent AE becomes more severe or lessens in severity, the highest severity should be recorded on the AE page of the eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on the AE page of the eCRF.

10.3.3.4. Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the AE page for the eCRF. Abnormal laboratory values will be reported as an AE if the:

- Laboratory finding requires an adjustment in the study drug(s) or discontinuation of treatment
- Laboratory finding requires additional testing (excludes retesting for spurious results) or surgical intervention
- Laboratory result or finding is associated with accompanying symptoms
- Laboratory result is considered to be an AE by the Investigator

10.4. Reporting Adverse Events

Each subject will be monitored for the occurrence of AEs from signing of the ICF through the final study visit. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. The Sponsor will determine the expectedness for an AE, which will be assessed using the current IB.

According to federal regulations, an Investigator must immediately report (within 24 hours of initial receipt of information) to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or IB, and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor (See 21 CFR 312.64(b)).

According to federal regulations, the Sponsor must notify the FDA and all participating Investigators as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that a potential serious risk arising from a clinical study qualifies for reporting. The Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event (See 21 CFR 312.32(c)(1)).

Furthermore, the Sponsor must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information (See 21 CFR 312.32(c)(2)).

10.4.1. Serious Adverse Event Reporting – Procedures for Investigators

All SAEs occurring from the time of informed consent through the final study visit must be reported to the Sponsor (or designee) within 24 hours of the Investigator's first knowledge of the event and regardless of the assessment of causality. Pregnancies will also be reported according to these timelines. Appropriate reporting forms are specified in the MOP.

All SAEs that the Investigator considers related to study drug and that occur at any time after study completion must be reported to the Sponsor (or designee).

The Investigator will follow SAEs until resolution regardless of whether the subject is still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects
- Return to baseline for a preexisting condition
- Laboratory values return to baseline or stabilize
- Investigator does not expect any further improvement or worsening of the event
- Fatal outcome—if an autopsy is performed, the autopsy report must be provided to the Sponsor as soon as it is available

Follow-up information regarding all SAEs must be reported within 24 hours, using the same procedure described above for initial reporting of SAEs.

10.4.2. Reporting Pregnancies and *In Utero* Drug Exposure

Pregnancy is not an AE. However, if a female subject, or female partner of a male subject, becomes pregnant during the conduct of the study or up to 90 days after the subject's last dose of IP, the Investigator must notify the Sponsor (or designee) within 24 hours of the Investigator's knowledge of the pregnancy. The Investigator must complete the Pregnancy Notification Form and submit to the Sponsor (or designee) per the procedures described in Section 10.4.1.

If pregnancy occurs in a female study subject, study treatment must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. If pregnancy occurs in the female partner of a male study subject, permission to follow her pregnancy will be sought.

The Investigator will follow the pregnant woman until completion of the pregnancy and must notify the Sponsor (or designee) of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. The Investigator will provide pregnancy outcome information on the

Pregnancy Outcome Report Form and submit it according to timelines described in Section 10.4.1. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant subject experiences an SAE during pregnancy, or the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs as outlined in Section 10.4.1.

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor (or designee). In addition, any infant death or congenital anomaly occurring after 30 days of birth that the Investigator suspects is related to the *in utero* exposure to the IP should also be reported as an SAE to the Sponsor (or designee).

10.4.3. Reporting of Serious Adverse Events to Institutional Review Boards

The Sponsor (or designee) shall notify the Investigator of potential serious risks from clinical studies, or any other sources, including the following:

- SAEs that are unexpected and related and submitted to the Health Authority.
- Any findings from other studies that suggest a significant risk in humans exposed to the drug.
- Any finding from animal or *in vitro* testing that suggest a significant risk to humans exposed to the drug, such as mutagenicity, teratogenicity, or carcinogenicity; or report of significant organ toxicity at or near the expected human exposure.

The Investigator will be responsible for submitting all reports of potential serious risks, described above, to their Institutional Review Board (IRB).

The Investigator must comply with the applicable regulatory requirements and timelines related to the reporting of SAEs to IRBs. The Investigator must keep copies of all SAE information, including correspondence with the Sponsor and the IRB on file.

11. STATISTICAL CONSIDERATIONS

[redacted]

11.1. General Considerations

Data will be summarized and tabulated using SAS® statistical analysis software. Descriptive statistics will be utilized for all safety and efficacy parameters. Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Safety and efficacy data will be compared over time to assess change from baseline during treatment and follow-up. Unless otherwise specified, baseline value is defined as the last non-missing measurement before administration of double-masked IP. Dose level differences will be assessed using appropriate parametric or non-parametric significance tests, as applicable. Analyses will be conducted for the study eye and for the fellow eye as deemed appropriate.

11.1.1. Handling Missing Data and Outliers

Unevaluable Values

- For laboratory and biomarker analysis, results of a non-numeric qualifier (e.g., "< x" - below the lower limit of quantification or "> x" - above the upper limit of quantification) will be displayed in the data listings as shown in the data, but the numerical value of "x" will be used for calculation of summary statistics.

Missing/Partial Dates

- In cases of missing or incomplete dates for safety data (e.g., AE or CMs), the actual data values as they appear in the original eCRFs will be presented in the data listings. The missing portion(s) will be assumed as the most conservative value possible, if deemed appropriate.

Missing Efficacy Measurements and Intercurrent Events

- Receipt of rescue therapy: Drusen volume, BCVA, and LLVA measurements after receipt of rescue therapy will be considered as missing. Receipt of rescue therapy in the study eye is considered to be disease progression.
- Missing BCVA or LLVA score: Missing data will be considered missing at random (MAR) with the analysis using a mixed-effects model for repeated measures (MMRM) analysis.
- Missing SD-OCT and/or FAF: Missing SD-OCT and/or FAF for the progression evaluation will be considered an indication of disease progression.

11.2. Statistical Hypotheses

The study is designed to show the superiority of QA102 over placebo in terms of drusen volume, BCVA, and LLVA.

The hypothesis for the primary and key secondary endpoints is that at least 1 dose regimen of QA102 is superior to placebo with respect to the mean change from baseline in the study eye at

Month 12. The hypotheses for each dose level of QA102 compared with placebo can be written as:

$$H_0: m_{QA,Post\text{-}dose} - m_{QABaseline} = m_{PL,Post\text{-}dose} - m_{PL,Baseline}$$

$$H_A: m_{QA,Post\text{-}dose} - m_{QA,Baseline} > m_{PL,\ Post\text{-}dose} - m_{PL,Baseline}$$

where m_{QA} and m_{PL} represent the mean values at baseline and post-dose visit for each dose level of QA102 and placebo, respectively.

Additionally, the hypothesis for each dose level of QA102 compared with placebo with respect to the mean rate of growth (slope) from baseline in square root area of GA lesion can be written as:

$$H_0: \beta_{QA} = \beta_{PL}$$

$$H_A: \beta_{QA} < \beta_{PL}$$

where β_{QA} and β_{PL} represent the mean rate of growth (slope) for each dose level of QA102 and placebo, respectively.

[redacted]

11.3. Determination of Sample Size

Approximately 150 subjects (50 per treatment group) will be treated to obtain 120 evaluable

[redacted]

11.4. Analysis Sets

11.4.1. Safety Analysis Set

The Safety (SAF) Analysis Set will include all randomized subjects who received any study medication. Subjects will be grouped by the actual treatment received.

11.4.2. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who received any study medication and who provided a baseline BCVA measurement and at least 1 post-baseline BCVA measurement. Subjects will be grouped by randomized treatment.

11.4.3. Efficacy-Evaluable Analysis Set

The Efficacy-Evaluable Analysis Set (EAS) will include all subjects in the FAS who completed 12 months of treatment or who discontinued earlier due to disease progression and had no major protocol deviations. Subjects will be grouped by randomized treatment.

11.5. Efficacy Analysis

Unless otherwise noted, summaries of efficacy will be presented by study eye for primary and key secondary endpoints, and by study eye and/or fellow eye for other secondary endpoints, as appropriate.

11.5.1. Primary Efficacy Analyses

The analysis for change from baseline in drusen volume in the study eye at Month 12 will be based on an MMRM model to compare the treatment groups. The MMRM model will include baseline GA status (naïve versus non-naïve), treatment, time, and treatment by time interaction as fixed effects, and baseline as a covariate. Time ordering will be treated as a repeated measure within subjects, and an unstructured covariance matrix is assumed. In case the model will not converge with the unstructured covariance structure, heterogeneous compound symmetry will be used instead. Furthermore, if the model fails to converge with heterogeneous compound symmetry, the heterogeneous Toeplitz (TOEPH) structure will be used. If the unstructured covariance structure will be used, the denominator degrees of freedom will be computed using the Kenward-Roger (1997) method. The estimates of treatment effects will be provided along with corresponding two-sided 90% confidence intervals (CIs) and p-value. MMRM analysis does not require data imputation and uses only the observed data. The treatment effects estimated with MMRM are valid under the assumption of MAR. To assess the robustness of the efficacy results, selected sensitivity analyses will be performed to assess the potential magnitude and direction of the impact of missing data.

11.5.2. Secondary Efficacy Analyses

Analyses for change from baseline in BCVA and LLVA in the study eye will proceed in the same manner as the analyses for the primary efficacy endpoint.

MMRM models also will be used to estimate the GA growth rate and its 90% CI. Mean rate of GA growth in mm^2/year and the mean rate of growth in mm/year from square root transformation of GA area in mm^2/year will be evaluated separately.

Similar analyses will be applied to other secondary endpoints with change from baseline measurements.

The frequency and percentage of subjects with disease progression in the study eye will be summarized and compared using the stratified Cochran-Mantel-Haenszel (CMH) test controlling for baseline GA status (naïve versus non-naïve). A subject receiving any rescue (anti-VEGF)

therapy during the study will be considered to have progression. Furthermore, the differences in proportions between two treatment groups and two-sided 90% exact confidence interval (CI) will be estimated. In addition, time to progression will be assessed using the Cox proportional hazard model (Cox PH) that includes the main effects for treatment and baseline GA status (naïve versus non-naïve). Estimates for other response endpoints are similar to those proposed for the disease progression.

11.6. Safety Analysis

No formal statistical analyses are planned for the safety data. All safety data will be listed by subject.

11.6.1. Analysis of Adverse Events

AEs will be coded by primary system organ class and preferred term using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) (version 24.1 or later). The number and percentage of subjects reporting treatment-emergent AEs will be tabulated for the SAF by MedDRA preferred term and system organ class with a breakdown by relationship to study drug and by severity. If there are any AEs leading to the discontinuation of the study or death, separate data listings will be generated.

11.6.2. Analysis of Clinical Laboratory Data

Laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits. Clinically significant worsening from baseline or new clinically significant laboratory test abnormalities that were considered by the Investigator to be AEs will be presented in the AE analyses. Clinical laboratory tests (observed values and change from baseline) will be summarized descriptively in tabular format.

A summary table of abnormal values of safety laboratory tests and all laboratory values reported as AEs will also be presented.

11.6.3. Vital Signs

Vital signs data will be presented for each subject and time point. Clinically significant worsening from baseline or new clinically significant vital sign findings that were considered by the Investigator to be AEs will be presented in the AE analyses. Observed values as well as change from baseline data will be summarized descriptively in tabular format.

11.6.4. Electrocardiogram

The 12-lead ECG will be performed at screening (Visit 1) and Month 15 (Visit 18). ECG data will be listed.

11.6.5. Slit Lamp Exam

The frequency and percentage of subjects with abnormalities as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for study eye and fellow eye.

11.6.6. Dilated Fundus Exam

The frequency and percentage of subjects with abnormalities as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for study eye and fellow eye.

11.7. Interim Analysis

An interim analysis will occur when roughly one-third of the total subjects are evaluable for the primary endpoint, change in drusen volume at Month 12. A futility monitoring of the change in drusen volume will be performed. The O'Brien-Fleming spending function is used to determine the futility test boundaries (Lan and DeMets 1983, O'Brien and Fleming 1979). The critical value for futility at interim is 0.494. The SAP will describe the planned interim analyses in greater detail.

The change in drusen volume, BCVA, and LLVA over time to Month 6 will be also evaluated.

The purposes of the interim analysis are to allow early stopping of the study for futility and to assess safety. An external, independent Data Review Committee (DRC) will review cumulative unmasked efficacy data and safety data and will have the responsibility to conduct a thorough safety assessment.

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Regulatory Issues, Ethical Concerns, and Study Oversight

12.1.1. Informed Consent Process

12.1.1.1. Consent/Assent Documents

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study intervention.

12.1.1.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed and dated informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.1.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigators, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension may include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Prohibitively slow subject enrollment
- Sponsor cancellation of drug development

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB, and/or FDA.

12.1.3. Confidentiality and Privacy

Participant confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality will be extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

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

The Medical Monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product will be able to inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (i.e., office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Lexitas Pharma Services, Inc. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Lexitas Pharma Services, Inc., research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Lexitas Pharma Services, Inc.

12.1.4. Future Use of Stored Specimens

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at Labcorp. These samples could be used to research the causes of AMD, its complications, and other conditions for which individuals with AMD are at increased risk, and to improve treatment. Labcorp will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through Labcorp.

12.1.5. Clinical Monitoring

Lexitas Pharma Services, Inc., will conduct the clinical monitoring for this study. A Clinical Monitoring Plan (CMP) is to be used, which will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.1.6. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practice, Good Manufacturing Practice).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

12.1.7. Data Handling and Record Keeping

12.1.7.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, CMs, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11–compliant data capture system provided by Lexitas Pharma Services, Inc. The data system includes password protection and internal quality checks,

such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.1.7.2. Study Records Retention

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 25 years, to meet international registration requirements. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

12.1.7.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or MOP requirements. The noncompliance may be on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site's Investigator to use continuous vigilance to identify and report deviations. Site-identified protocol deviations must be reported to the Clinical Research Associate (CRA). All deviations also must be addressed in study source documents and reported to the IRB (if applicable) and to Lexitas Pharma Services, Inc., and/or Sponsor. The site Investigator is responsible for knowing and adhering to the IRB reporting requirements.

12.1.7.4. Publication and Data Sharing Policy

All information concerning QA102, including but not limited to, Sponsor operations, patent applications, formulas, manufacturing processes, scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information solely for the purposes of carrying out this study and must not use it for other purposes without the Sponsor's advanced written consent.

The information developed in this study will be used by the Sponsor in connection with the continued development of QA102 and thus may be disclosed to other clinical Investigators or government regulatory agencies. The Investigator is obligated to provide the Sponsor with all data obtained in the study.

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14. APPENDICES

14.1. Appendix 1: Schedule of Assessments and Procedures

Visit Timing	Day -21 to -7[1] Screening	Day 1 Random-ization	Day 7	Month 1 Week 4 ± 3 days	Month 2 Week 8 ± 3 days	Month 3 Week 13 ± 3 days	Mo. 4, 5, 7, 8, 10, 11, 13, 14 Wk. 17, 21, 30, 34, 43, 47, 56, 60 ± 7 days	Month 6 Week 26 ± 7 days	Month 9 Week 39 ± 7 days	Month 12 Week 52 ± 7 days	Month 15 Week 65 ± 7 days End of Study/ET
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 10, 11, 13, 14, 16, 17 (Telephone)**	**9**	**12**	**15**	**18**
Informed Consent	X										
Inclusion/Exclusion	X	X									
Demographics and Iris Color	X										
Medical/Ophthalmic History	X										
CMs	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X		X	X	X	X
12-Lead Safety ECG	X										X
Body Weight	X										
UPT or FSH Test[2]	X							X		X	X
Blood/Urine Collection for Clinical Labs	X					X		X	X	X	X
BCVA (ETDRS)	X	X	X	X	X	X		X	X	X	X
LLVA	X	X	X	X	X	X		X	X	X	X
IOP	X	X	X	X	X	X		X	X	X	X
SD-OCT	X	(X)[3]		X	X	X		X	X	X	X
FAF	X	(X)[3]		X	X	X		X	X	X	X
Fundus Photography	X	(X)[3]		X	X	X		X	X	X	X
SLE	X	X	X	X	X	X		X	X	X	X

Visit Timing	Day -21 to -7[1] Screening	Day 1 Random-ization	Day 7	Month 1 Week 4 ± 3 days	Month 2 Week 8 ± 3 days	Month 3 Week 13 ± 3 days	Mo. 4, 5, 7, 8, 10, 11, 13, 14 Wk. 17, 21, 30, 34, 43, 47, 56, 60 ± 7 days	Month 6 Week 26 ± 7 days	Month 9 Week 39 ± 7 days	Month 12 Week 52 ± 7 days	Month 15 Week 65 ± 7 days End of Study/ET
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 10, 11, 13, 14, 16, 17 (Telephone)**	**9**	**12**	**15**	**18**
DFE	X	X	X	X	X	X		X	X	X	X
Study Eye Determination	X										
Symptoms/AEs	X	X	X	X	X	X	X	X	X	X	X
IP + Dosing Diary Dispensed		X		X	X	X		X	X	X	
IP + Dosing Diary Collected			X	X	X	X		X	X	X	X
Dosing Compliance Assessed			X	X	X	X		X	X	X	X

AE=adverse event; BCVA=best-corrected visual acuity; CMs=concomitant medications; CNV=choroidal neovascularization; CRC=central reading center; DFE=dilated fundus exam; ECG=electrocardiogram; ET=early termination; ETDRS=Early Treatment Diabetes Retinopathy Study; FAF=fundus autofluorescence; FSH=follicle-stimulating hormone; IOP=intraocular pressure; IP=investigational product; LLVA=low-luminance visual acuity; SD-OCT=spectral domain optical coherence tomography; SLE=slit lamp exam; UPT=urine pregnancy test; WOCBP=women of childbearing potential

[1] Although the subject must be seen for screening no later than Day -7, lab results may be received as late as Day 1.

[2] UPT for WOCBP at visits as marked. Post-menopausal women will undergo an FSH test at screening only.

[3] A significant decrease in BCVA from Visit 1 to Visit 2 may indicate an onset of CNV. In that case, the subject should repeat SD-OCT, FAF, and fundus photography. Randomization and Visit 3 will be delayed pending CRC reading.

14.2. Appendix 2: Creatinine Clearance Guidelines

For males:
Creatinine clearance (mL/min) = (140 - age) × weight (kg) / 0.814 × plasma creatinine (µmol/L)

For females:
Creatinine clearance (mL/min) = 0.85 × (140 - age) × weight (kg) / 0.814 × plasma creatinine (µmol/L)

(Cockcroft and Gault 1976)

Note: Variations include estimating ideal body weight from subject height in obese subjects.

14.3. Appendix 3: Contraception Guidelines and "Childbearing Potential" Definitions

The following guidance is adapted from the Clinical Trial Facilitation Group (2014).

Definitions of "Women of Childbearing Potential," "Women of Non-Childbearing Potential"

"Women of childbearing potential" are female subjects who are physiologically capable of becoming pregnant. Conversely, "women of non-childbearing potential" are defined as female subjects documented history of meeting any of the following criteria:

- Surgically sterile (i.e., through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy).
- Post-menopausal, defined as:
    - ≥55 years of age with no spontaneous menses for ≥12 months OR
    - <55 years of age with no spontaneous menses for ≥12 months AND with a post-menopausal FSH concentration >30 IU/mL.

Highly effective forms of birth control include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).

Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the subject's usual and preferred lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception. Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and, if used, this method must be combined with another acceptable method listed above.

14.4. Appendix 4: Investigator Agreement

A PHASE 2, DOUBLE-MASKED, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY ASSESSING THE SAFETY AND EFFICACY OF QA102 IN SUBJECTS WITH DRY AGE-RELATED MACULAR DEGENERATION (AMD)

(AMEND STUDY)

VERSION 4.0

[redacted]

I have read the clinical study protocol and understand it. I agree to conduct the study as outlined in this document and in accordance with Good Clinical Practice Guidelines, all local and federal requirements and regulations, and in compliance with those precepts set forth in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

Further, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Investigator:

Name (printed)	Signature	Date

14.5. Appendix 5: Compliance Statement

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and as stipulated in the Declaration of Helsinki (2013) with respect to the use of human subjects in clinical studies and investigations.

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Sponsor's Representative:

[redacted]

Name Signature Date

Medical Monitor:

[redacted]

Name Signature Date