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Clinical Study Phase 3 Protocol
OPI-NYXP-302
VEGA-3

Randomized, Double-Masked, Placebo-Controlled, Multicenter, Phase 3 Study of the Efficacy and Safety of Phentolamine Ophthalmic Solution (POS) 0.75% in Participants With Presbyopia

Ocuphire Pharma, Inc.
37000 Grand River Avenue, Suite 120
Farmington Hills, MI 48335

Original: **14 June 2024**
Amendment No. 1: **01 July 2024**
Amendment No. 2: **19 July 2024**

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Study Title:	Randomized, Double-Masked, Placebo-Controlled, Multicenter, Phase 3 Study of the Efficacy and Safety of Phentolamine Ophthalmic Solution (POS) 0.75% in Participants With Presbyopia
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Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Ocuphire Pharma, Inc.

George Magrath, MD, MBA, MS
CEO
Ocuphire Pharma, Inc.
[redacted]

Signature

Date

Charles Slonim, MD
Medical Monitor
Oculos Development Services, LLC
[redacted]

Signature

Date

INVESTIGATOR'S AGREEMENT

OPI-NYXP-302
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Original Protocol: 14 June 2024
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Investigator Agreement:

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki, and with the U.S. Code of Federal Regulations governing electronic records; electronic signatures (21 CFR 11), the protection of human subjects (21 CFR 50), financial disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), and the obligations of Clinical Investigators (21 CFR 312).

Signature: _____ Date: _____

Printed Name: _____

PROCEDURES IN CASE OF EMERGENCY

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1 STUDY SUMMARY

Study Number	OPI-NYXP-302 (VEGA-3)
Clinical Phase	Phase 3
Type of Study	Randomized, double-masked, placebo-controlled, multicenter study of the efficacy and safety of Phentolamine Ophthalmic Solution (POS) 0.75% in participants with presbyopia
Name of Investigational Products	POS 0.75% Eye Drops
Duration of Study	Approximately 48 weeks
Study Objectives	The VEGA-3 study is a randomized, double-masked, placebo-controlled, multiple-dose study of the safety and efficacy of POS in participants with presbyopia. The primary objective of this study is: • To evaluate the efficacy of POS to improve distance-corrected near visual acuity (DCNVA) without loss of best-corrected distance visual acuity (BCDVA) compared to placebo in participants with presbyopia Secondary objectives of this study are: • To evaluate additional efficacy measures, such as visual acuity (VA) and pupil diameter (PD), across multiple time points and visits for POS in participants with presbyopia • To evaluate tachyphylaxis of the DCNVA response to POS after 6 weeks of dosing • To evaluate the effect of iris color, baseline PD, and baseline DCNVA on the efficacy of POS in participants with presbyopia • To evaluate the ocular and systemic safety of POS in participants with presbyopia • To evaluate participant-reported outcomes of POS in participants with presbyopia
Design	This is a randomized, double-masked, placebo-controlled, multicenter, Phase 3 study in approximately 545 participants with presbyopia. On Day -7 to -1 (Screening), participants will be assessed for eligibility.

	On Day 1 (Baseline), participants will be reassessed for all VA measurements and, if eligibility is met, will be randomized 3:2 to 1 of 2 treatment arms: • Daily evening POS (n=327) • Daily evening placebo (ie, POS vehicle; n=218) Randomization will be stratified by iris color (light/dark irides). The study eye is defined as the eligible eye with the worse baseline DCNVA at Visit 2 (Day 1; Baseline). If both eyes have the same baseline DCNVA, then the eye with the better BCDVA will be the study eye. If both DCNVA and BCDVA are equivalent between eyes, the study eye will be the right eye. The study eye and fellow eye will both be evaluated with all assessments. For all assessments other than VA, the baseline values will be determined during screening assessments at Visit 1. For PD and VA measurements, assessments at Visit 2 will be used to determine baseline values. Study medication will be administered as a single drop in each eye by site staff on Day 1 (Visit 2; Baseline). Starting Day 2, study medication will be self-administered by the participant for approximately 48 weeks as a single drop in each eye in the evening near bedtime. On the evening prior to each office visit, participants should dose as close as possible to 12 hours prior to the scheduled time for each office visit (Visits 3 through 12).
Participant Population	Approximately 545 randomized participants with presbyopia
Inclusion Criteria	Participants must meet all of the following criteria: 1. Males or females ≥ 45 and ≤ 64 years of age 2. Able to comply with all protocol-mandated procedures independently and to attend all scheduled office visits 3. Able and willing to give signed informed consent 4. Able to self-administer study medication throughout the study period ***Inclusion criteria #5, #6, and #7 must all be met at both Screening and Baseline Visits:*** 5. BCDVA of 55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/20 Snellen equivalent) or better in photopic conditions in each eye 6. DCNVA of 50 ETDRS letters (20/50 Snellen equivalent) or worse but not <35 ETDRS letters (20/100 Snellen equivalent) in photopic conditions in each eye and binocularly 7. For participants who depend on reading glasses or bifocals, binocular best-corrected near VA of 65 ETDRS letters (20/25 Snellen equivalent) or better

	8. Photopic PD of ≥ 4 mm in the study eye at Screening
Exclusion Criteria	Excluded from the study will be individuals with any of the following characteristics: **Ophthalmic (in either eye):** 1. Use of any topical prescription (including Vuity® or Qlosi™) or over-the-counter (OTC) ophthalmic medications of any kind within 7 days of Screening until study completion, with the exception of lid scrubs with OTC products (eg, OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.) and artificial tears as specified in Exclusion Criterion #2 below 2. Use of any OTC artificial tears (preserved or unpreserved) during visit days or 15 min before or after instillation of study medication 3. Use of Ryzumvi™ (POS) within 7 days prior to Screening 4. Use of any dry eye product, such as topical ophthalmic therapy for dry eye (eg, generic cyclosporine, Restasis®, Xiidra®, Cequa®, Eysuvis®, and Meibo®) or intranasal dry eye product (eg, Tyrvaya®) or other devices within 12 months prior to Screening 5. Tear break-up time of < 5 seconds or corneal fluorescein staining (CFS) Grade ≥ 2 in the inferior zone or Grade ≥ 1 in the central zone using the National Eye Institute scale 6. Clinically significant ocular disease (eg, cataract, glaucoma, corneal edema, uveitis, retinal degeneration, loss of visual field, or any macular pathology) that, in the judgment of the Investigator, might interfere with study procedures 7. Recent or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, keratitis, etc.). Participants must be symptom free for at least 7 days prior to Screening 8. Any history of herpes simplex or herpes zoster keratitis 9. Known allergy, hypersensitivity, or contraindication to any component of the phentolamine or vehicle formulations 10. Prior participation in a study involving the use of POS for the treatment of presbyopia or night vision disturbance 11. History of cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal 12. Ocular trauma within 6 months prior to Screening 13. Ocular surgery or any ocular laser treatment within 6 months prior to Screening. Any history of radial keratotomy is prohibited

14. Participants with surgical monovision, multifocal, or extended depth-of-focus intraocular lenses (IOLs). Monofocal IOLs are acceptable if in place > 6 months prior to Screening
15. Monofocal IOL in place > 6 months prior to Screening with any posterior capsule opacification
16. History of any traumatic (surgical or nonsurgical) or nontraumatic condition affecting the pupil or iris (eg, irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy, iridectomy, iritis, etc.)
17. Unwilling or unable to discontinue use of contact lenses at least 1 hour prior to Screening for soft contact lenses or at least 8 hours prior to Screening for hard gas permeable contact lenses, and at least 8 hours (for both types of lenses) prior to all other office visits

Systemic:

18. Known hypersensitivity or contraindication to alpha- and/or beta-adrenoceptor antagonists (eg, chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure (BP) or heart rate (HR); second- or third-degree heart blockage or congestive heart failure)
19. Known hypersensitivity or contraindication to any systemic cholinergic parasympathomimetic agent
20. Clinically significant systemic disease (eg, uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere with the study as deemed by the judgment of the Investigator
21. Initiation of treatment with, or any changes to, the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs within 7 days prior to Screening or during the study; however, Flomax® (tamsulosin) is specifically excluded
22. Participation in any investigational study within 30 days prior to Screening
23. Females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device, hormonal contraception (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. A female is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post–surgical sterilization. All females of childbearing potential, including those with post−tubal ligation, must have a negative urine pregnancy test result at Visit 1 (Screening)

	24. Resting HR outside the range of 50 to 110 beats per min (bpm) following at least a 5-min rest period in the sitting position at Visit 1 (Screening). HR may be repeated **only once** if outside the specified range, following another 5-min rest period in the sitting position 25. Hypertension with resting diastolic BP > 105 mmHg or systolic BP > 160 mmHg following at least a 5-min rest period in the sitting position at Visit 1 (Screening). BP may be repeated **only once** if outside the specified range, following another 5-min rest period in the sitting position
Study Assessments	• Manifest refraction and near add • BCDVA [redacted] • Distance-corrected intermediate visual acuity (DCIVA) [redacted] • DCNVA [redacted] • PD [redacted] • Slit lamp biomicroscopy • Automated corneal specular microscopy (at select sites) • Intraocular pressure (IOP) • Direct or indirect ophthalmoscopy without dilation • Urine pregnancy test for females of childbearing potential • HR and BP • Participant questionnaire • Tear break-up time and CFS (for eligibility only)
Number of Investigational Sites	Approximately 40 sites
Statistical Methods	Sample size Using $\alpha = 0.05$ significance and a two-tailed test, 525 evaluable participants (313 participants each in the POS arm and 212 participants in the placebo arms) who are evaluable for efficacy will provide greater than 90% power to detect a difference of 11.5% between treatments in percentage of participants with ≥ 15 letters of improvement in photopic binocular DCNVA and with < 5 letters of loss in photopic binocular BCDVA from baseline at 12 hours post-dose at Visit 4 (Day 8). [redacted] An additional 20 participants will be enrolled to account for dropouts. Interim analyses

	The primary efficacy analysis of study data will be conducted after all participants complete Week 6 of the study. All efficacy and safety endpoints though Week 6, as well as the endpoint for tachyphylaxis, will be analyzed. Another interim analysis of safety endpoints will be conducted after all participants complete Month 6 of the study. [redacted]
Primary Efficacy Endpoint	The primary efficacy endpoint is the percentage of participants with ≥ 15 letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Visit 4 (Day 8). This comparison will be analyzed first using a hierarchical testing method.
Secondary Efficacy Endpoints	Secondary efficacy endpoints measured at various time points and visits, as specified in the Visit Schedule and Assessments, include: • Percentage of participants with ≥ 15 letters of improvement in binocular **DCNVA** and with < 5 letters of loss in binocular **BCDVA** from baseline (excluding primary outcome time point) • Percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement in **DCNVA** from baseline (monocular and binocular) • Change in **DCNVA** from baseline (monocular and binocular) • Change in mean binocular **DCNVA** from baseline at Week 6 compared to the best prior observed change from baseline in mean binocular **DCNVA** in participants treated with POS • Percentage of participants with **DCNVA** ≤ 20/15, ≤ 20/20, ≤ 20/25, ≤ 20/32, ≤ 20/40, ≤ 20/50, ≤ 20/63, ≤ 20/80, ≤ 20/100, ≤ 20/125, and ≤ 20/160 • Percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement in binocular **DCIVA** from baseline • Change in binocular **DCIVA** from baseline • Percentage of participants with loss or improvement in **BCDVA** from baseline (monocular and binocular) • Change in **BCDVA** from baseline (monocular and binocular) • Change and percent change in **PD** from baseline

	• Percentage of participants with **PD** of < 3.5, < 3.0, < 2.5, < 2.0, and < 1.5 mm • Percentage of participants with **PD** of 1.5 to < 2.0 mm, 2.0 to < 2.5 mm, 2.5 to < 3.0 mm, and 3.0 to < 3.5 mm • Percentage of participants with baseline **DCNVA** ≤ 20/63, ≤ 20/80, ≤ 20/100, ≤ 20/125, and ≤ 20/160, with a ≥ 10-letter and ≥ 15-letter improvement in **DCNVA** • Percentage of participants with baseline **DCNVA** from 20/50 to 20/63, 20/50 to 20/80, 20/50 to 20/100, 20/50 to 20/125, and 20/50 to 20/160, with a ≥ 10-letter and ≥ 15-letter improvement in **DCNVA** • Change from baseline in overall and component participant-reported outcomes All efficacy endpoints will be analyzed overall and by light/dark irides. Separate analyses will be performed for binocular, study eye, and fellow eye, where applicable. Unless otherwise noted, efficacy endpoints will be analyzed by the Modified Intention-to-Treat Population. Selected analyses will be performed on the Per Protocol Population as specified in the Statistical Analysis Plan (SAP). A subset of the secondary pairwise comparisons will be included in the hierarchical analysis as specified in the SAP.
Safety Endpoints	Safety measures are adverse events, IOP, BCDVA, slit lamp biomicroscopy, automated corneal specular microscopy, undilated ophthalmoscopy, and HR and BP. Urine pregnancy tests for females of childbearing potential will also be conducted.
Study Medications, Dose, and Mode of Administration	<u>0.75% Phentolamine Ophthalmic Solution:</u> For those participants randomized to POS, 1 drop of POS will be self-administered by the participant in each eye once daily (QD) in the evening near bedtime for approximately 48 weeks. <u>Placebo (POS vehicle):</u> For those participants randomized to placebo, 1 drop of POS vehicle will be self-administered by the participant in each eye QD in the evening near bedtime for approximately 48 weeks. Study medication doses taken the evening prior to an in-office visit should be administered as close as possible to 12 hours prior to the scheduled time for that office visit.

TABLE OF CONTENTS

INVESTIGATOR'S AGREEMENT 3
PROCEDURES IN CASE OF EMERGENCY 4
1 STUDY SUMMARY 5
TABLE OF CONTENTS 12
LIST OF TABLES 14
2 ABBREVIATIONS AND TERMS 15
3 INTRODUCTION 17
3.1 Investigational Products 17
3.2 Findings From Nonclinical and Clinical Studies 17
3.3 Design Justification 17
4 OBJECTIVES AND PURPOSE 21
5 STUDY DESIGN 22
5.1 Primary Endpoint 22
5.2 Secondary Endpoints 22
5.3 Description and Schedule of Visits and Procedures 24
5.3.1 Visit 1 (Screening)/Day -7 to -1 27
5.3.2 Visit 2 (Baseline)/Day 1 27
5.3.3 Visit 3/Day 3 27
5.3.4 Visit 4/Day 8 ± 1 day 28
5.3.5 Visit 5/Week 6 ± 3 days 28
5.3.6 Visit 6/Week 12 ± 3 days 29
5.3.7 Visit 7/Week 18 ± 3 days 29
5.3.8 Visit 8/Week 24 ± 3 days 29
5.3.9 Visit 9/Week 30 ± 3 days 30
5.3.10 Visit 10/Week 36 ± 3 days 30
5.3.11 Visit 11/Week 42 ± 3 days 31
5.3.12 Visit 12 (End of Study)/Week 48 ± 3 days 31
5.3.13 Unscheduled Visits 31
5.3.14 Visit Variation 31
5.4 Measures Taken to Minimize/Avoid Bias 32
5.5 Study Medications 32
5.5.1 Packaging and Labeling 33
5.5.2 Storage of Study Medication and Dispensing 33
5.5.3 Study Medication Administration 33
5.5.4 Study Medication Accountability 33
5.5.4.1 Receipt and Disposition of Study Medication 33
5.5.4.2 Return of Study Medication by Study Site 34
5.6 Expected Duration of Participant Participation 34

5.7 Randomization and Procedure for Breaking the Code 34
5.8 Collection of Data 35
5.9 Completed Participant 35
5.10 Non-Completing Participant 35
5.10.1 Study Medication Discontinuation 35
5.10.2 Reasons for Withdrawal From Study 35
5.10.3 Entire Study Terminated 36
5.10.4 Actions After Discontinuation 36
5.11 Completed Study 36
6 PARTICIPANT INCLUSION AND EXCLUSION CRITERIA 37
6.1 Participant Inclusion Criteria 37
6.2 Participant Exclusion Criteria 37
7 TREATMENT OF PARTICIPANTS 40
7.1 Treatment Adherence 40
7.2 Concomitant Medications 40
8 ASSESSMENT OF EFFICACY 42
8.1 Specification of the Efficacy Parameters 42
8.2 Assessing, Recording, and Analyzing Efficacy Parameters 42
9 ASSESSMENT OF SAFETY 43
9.1 Specification of Safety Parameters 43
9.2 Adverse Events and Serious Adverse Events 43
9.2.1 Adverse Event Definitions 43
9.2.2 Follow-Up of Participants After Adverse Events 47
10 STATISTICS 48
10.1 Sample Size 48
10.2 Analysis Populations 48
10.3 Statistical Methods 48
10.3.1 General Considerations 48
10.3.2 Demographic and Baseline Characteristics 48
10.3.3 Participant Disposition 49
10.3.4 Medical History and Prior/Concomitant Medications 49
10.3.5 Estimands for Efficacy 49
10.3.6 Analysis of Efficacy 50
10.3.7 Analysis of Safety 51
10.4 Interim Analyses 52
10.5 Procedure for Accounting for Missing, Unused, or Spurious Data 52
10.6 Procedure for Reporting Deviations From the Statistical Plan 52
11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS 53
12 QUALITY CONTROL AND QUALITY ASSURANCE 54

13 ETHICAL CONSIDERATIONS AND GOOD CLINICAL PRACTICE COMPLIANCE....55
13.1 Good Clinical Practice Compliance....55
13.2 Institutional Review Board....55
13.3 Protocol Deviations/Violations....55
13.4 Informed Consent Requirements....55
14 DATA HANDLING AND RECORD KEEPING....57
14.1 Data Entry....57
14.2 Data Quality Control and Reporting....57
14.3 Archiving of Data....57
14.4 Records Retention....57
14.5 Amendments to the Protocol....57
15 SUMMARY OF CHANGES....58
16 BIBLIOGRAPHY....59
APPENDIX 1: IRIS COLOR CHART....61
APPENDIX 2: PARTICIPANT QUESTIONNAIRE FOR BASELINE VISIT....62
APPENDIX 3: PARTICIPANT QUESTIONNAIRE FOR VISITS 3, 4, AND 5...64
APPENDIX 4: ADRENERGIC AND CHOLINERGIC DRUGS....66

LIST OF TABLES

Table 1 Visit Schedule and Assessments....25
Table 2 Phentolamine Mesylate Drug Substance and Drug Product Identifiers....32

2 ABBREVIATIONS AND TERMS

Abbreviation	Full term
°C	degrees Celsius
°F	degree Fahrenheit
AE	adverse event
ANCOVA	analysis of covariance
ARP	All Randomized Population
BCDVA	best-corrected distance visual acuity
BP	blood pressure
bpm	beats per min
CFS	corneal fluorescein staining
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	contract research organization
D	diopter
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IOL	intraocular lens
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	Intention-to-Treat

LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
OTC	over-the-counter
OU	oculus uterque (both eyes)
PD	pupil diameter
POS	0.75% Phentolamine Ophthalmic Solution or 1% Phentolamine Mesylate Ophthalmic Solution
PP	Per Protocol
QD	once daily
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
TBUT	tear break-up time
TEAE	treatment-emergent adverse event
US	United States
USP	United States Pharmacopeia
VA	visual acuity

3 INTRODUCTION

3.1 Investigational Products

The test product is 0.75% Phentolamine Ophthalmic Solution (POS) Eye Drops, a non-selective alpha-1 and alpha-2 adrenergic antagonist. Note that the concentration of 0.75% refers to phentolamine free base and is the same as and used in place of 1% phentolamine mesylate drug substance, which was how POS had been described in all prior studies. Placebo control is POS vehicle alone.

3.2 Findings From Nonclinical and Clinical Studies

Detailed findings from nonclinical and clinical studies for phentolamine mesylate or phentolamine ophthalmic solutions and potential risk are provided in the POS Investigator's Brochure (IB; POS IB 2022).

POS has been studied in a total of 12 clinical trials (three Phase 1, five Phase 2, and four Phase 3) enrolling over 1,100 participants (including participants 3 years of age and up, with over 650 participants treated with POS) and has demonstrated promising clinical data for use in multiple ophthalmic indications.

In prior clinical trials, POS has demonstrated a consistent ability to decrease pupil diameter (PD) by approximately 20% to 30% (~1–1.5 mm) in both mesopic and photopic conditions (McDonald 2010; Holladay 2018; Pepose 2020). POS was found to be efficacious for over 24 hours, with an onset of action of approximately 30 to 60 min. POS was well tolerated at single doses and multiple doses up to 14 days. Safety of the participants in these trials was evaluated by adverse event (AE) monitoring, physical examinations, and vital sign assessments. Across all trials, no serious adverse events (SAEs) have been reported. No deaths occurred in any of the trials. No clinically meaningful changes were observed in physical examinations or vital signs, including blood pressure (BP) and heart rate (HR). Adverse events reported were mild to moderate in intensity, with the most common being transient conjunctival hyperemia (eye redness), ocular irritation, and dysgeusia; however, POS dosing near bedtime was observed to mitigate or minimize these side effects during the daytime.

3.3 Design Justification

Presbyopia is an age-related condition, with onset most common in people over 40 years old (AOA). Patients experience blurred near vision, difficulty seeing in dim light, and eye strain. In young, healthy eyes, human crystalline lenses are able to focus light from objects at different distances by a process called accommodation. During accommodation, the ciliary muscle surrounding the lens contracts, causing the lens to change shape, thus increasing the focusing power of the eye. This allows for dynamic, clear vision at both near and far distances. With increasing age, the lens becomes stiffer, which limits the eye's ability to adjust its focus for reading or for other tasks that require clear vision at near distances.

Presbyopia has a significantly negative impact on quality of life (Martinez 1998), interfering with daily activities such as reading, use of computers or hand-held devices, and seeing the dashboard of a car. It is estimated that 100 million Americans have presbyopia, and this number is expected to grow as the population above the age of 40 increases (McDonald 2010).

Limitations of Existing Treatments for Presbyopia

Vuity™ (PCH 1.25%) has recently been approved for the treatment of presbyopia. In two Phase 3 studies, Vuity met its primary outcome measure, with 31% and 26% of Vuity-treated participants gaining 3 or more lines of mesopic distance-corrected near visual acuity (DCNVA) 3 hours post-dose compared to 8% and 11% of placebo-treated participants. However, limitations to Vuity include limited duration of efficacy, with a need for twice daily dosing to achieve efficacy throughout the day; headache, browache, and burning/stinging associated with drug administration; accommodative spasm and risk of angle-closure glaucoma due to activation of the ciliary muscle; and risk of retinal detachment in participants with high myopia (Monestam 2006).

Qlosi (0.4% pilocarpine) has also been recently approved for presbyopia. Qlosi was evaluated in 309 patients with presbyopia in 2 randomized, double-masked, vehicle-controlled studies (NEAR-1 and NEAR-2) of 15 days duration. The most commonly reported treatment-related AEs in 5% to 8% of patients were instillation site pain and headache. Ocular adverse reaction reported in 2% to 5% of patients was blurred vision. The majority of the AEs were mild, transient, and self-resolving. Like Vuity, use of Qlosi has associated risk of accommodative spasm and retinal detachment (Holland 2024).

Other available treatments for presbyopia include reading glasses, bifocals, gradients, bifocal contact lenses, and multifocal intraocular lenses (IOLs). Reading glasses can be inconvenient and must be taken off and put on frequently throughout the day to see objects at far and near distances, respectively. Many patients express frustration with losing or forgetting their reading glasses. Moreover, some patients find glasses unflattering, and contact lenses for presbyopia have their own set of drawbacks regarding eye strain and limitation of use.

A small portion of patients elect surgical intervention, including laser treatment, to achieve monovision. The risks of such interventions include a potential decrease in contrast sensitivity and stereopsis and the creation or worsening of dim light vision disturbances.

POS Opportunity in Presbyopia

Pharmacological treatment of presbyopia is a promising strategy and an intense area of focus by several pharmaceutical companies. Other pharmacological and device approaches have consistently demonstrated that reducing pupil size to a diameter of approximately 2 to 3 mm will lead to significant improvement in presbyopia symptoms by increasing depth of focus (Pepose 2020; Pop 2004; POS IB 2022). In multiple trials, it has been shown that POS reduces PD by approximately 20% to 30% and improves near visual acuity (VA) for at least 24 hours after a single application. OPI-NYXP-201 (VEGA-1) was a 7-day (2 visits), double-masked, randomized, placebo-controlled, multicenter Phase 2 trial in 150 presbyopic participants. Study OPI-NYXP-301 (VEGA-2) was a randomized, placebo controlled, multicenter Phase 3 clinical trial to assess the efficacy and safety of POS and POS with adjunctive LDP to treat presbyopia. The study was conducted in 2 stages. In the first stage, 333 participants were randomized 1:1 to receive once daily (QD) evening POS or placebo for 7 days. In the second stage, participants in the POS group and placebo group were randomized to receive morning LDP or placebo adjunctive to their evening POS or placebo. The primary outcome measure was the percentage of participants who gained ≥ 15 letters of DCNVA without losing ≥ 5 letters of BCDVA after

7 days of dosing. Eligible participants were 40 to 64 years old, had BCDVA of 20/25 or better in each eye, had DCNVA between 20/50 and 20/100 in each eye and binocularly, had best-corrected near VA of 20/25 or better, and had PD of ≥ 3 mm under photopic conditions. A summary of the results of the VEGA-1 and VEGA-2 studies is presented here.

Results From the VEGA-1 Study:

POS as a Single Agent

Following 3 to 4 days of treatment with POS or placebo, 30.1% of POS-treated participants had ≥ 15 letters of improvement in photopic binocular DCNVA compared with 13.5% of placebo-treated participants 12 hours after the last dose (p=0.0265). This benefit remained stable over the next 6 hours, with a mean of 36.7% of POS-treated participants improving by 15 or more letters DCNVA 18 hours post-dose. [redacted] Significantly more participants treated with POS achieved binocular DCNVA of 20/40 or better compared with placebo (56% vs 36%, respectively; p=0.0080).

POS + LDP as Adjunctive Therapy

A statistically significantly greater number of participants in the Per Protocol (PP) Population treated with POS + LDP had ≥ 15 letters of improvement in photopic binocular DCNVA at 1 hour post-LDP treatment (primary endpoint) compared with placebo alone (60.45% vs 27.9%, respectively; p=0.0037). In addition, the POS + LDP arm had significantly more participants with ≥ 15 letters of improvement in photopic binocular DCNVA compared with placebo alone at all timepoints from 30 min through 4 hours post-LDP treatment (p≤0.0166 for each). This benefit was retained for all timepoints between 30 min and 4 hours when requiring that participants with ≥ 15 letters of improvement in photopic binocular DCNVA also had to have < 5 letters of loss in photopic binocular best-corrected distance visual acuity (BCDVA), the accepted registration endpoint. The benefit of LDP adjunctive therapy to POS was consistent regardless of iris color.

The effect of POS + LDP on DCNVA was rapid and clinically significant. By 30 min post-LDP treatment, 79% of participants had photopic binocular DCNVA of 20/40 or better. By 1 hour post-LDP treatment, 84% of participants had binocular DCNVA of 20/40 or better. Significantly more participants treated with LDP adjunctive to POS had photopic binocular DCNVA 20/40 or better compared with placebo at 30 min through 2 hours (p≤0.0119 for each).

POS + LDP treatment resulted in more participants achieving a ≥ 15-letter improvement in DCNVA compared with each of its components used individually at all timepoints from 30 min to 2 hours post-LDP treatment. Although the study was not statistically powered for this outcome, the percent of responders at 30 min with combination therapy (61%) was significantly greater than the response rate with LDP alone (26%; p=0.0076) or POS alone (33%; p=0.0265).

Safety Results From the VEGA-1 Study

POS, when administered with LDP as adjunctive therapy or as a single agent, was well tolerated in this study. Fifty treatment-emergent adverse events (TEAEs) were reported in 15 participants (34.1%) treated with POS + LDP, 4 TEAEs were reported in 2 participants (4.4%) treated with placebo alone, 18 TEAEs were reported in 6 participants (20.0%) treated with POS alone, and 13 TEAEs were reported in 6 participants (19.4%) treated with placebo + LDP One participant in the POS + LDP arm had 2 TEAEs (mild conjunctival hyperemia and mild eye irritation) leading both to study medication discontinuation and withdrawal from the study. No participants had any serious TEAEs, and no participants died during the study.

Results From the VEGA-2 Study:

POS as a Single Agent

A significantly greater percentage of participants treated with POS gained ≥ 15 letters of binocular DCNVA without losing ≥ 5 letters of BCDVA 12 hours after 7 days of dosing (23% vs 11%, $p<0.01$). The effect was durable lasting up to 20 hours post-dose.

POS + LDP as Adjunctive Therapy

Forty-four percent of participants treated with POS + LDP for 7 days gained ≥ 15 letters of binocular DCNVA without losing ≥ 5 letters of BCDVA when measured 30 minutes after LDP administration, compared to 21% of placebo-treated participants ($p<0.01$). POS + LDP was also statistically significantly better than placebo + LDP (44% vs 28%; $p<0.05$). However, no significant difference in percentage of participants who responded was obtained between POS + LDP and POS + placebo (44% vs 43%; $p=0.81$). Due to the failure of adjunctive therapy to show a statistically significant increase in efficacy over POS monotherapy, only POS monotherapy will be studied in the current trial.

Safety Results From the VEGA-2 Study

POS, when administered with LDP as adjunctive therapy or as a single agent, was well tolerated in this study. Thirty TEAEs were reported in 13 participants (16.5%) treated with POS + LDP. In Stage 1, 78 TEAEs were reported in 40 participants (24.4%) treated with placebo alone and in Stage 2, 22 TEAEs were reported in 13 participants (15.9%) treated with placebo. In participants treated with POS alone, 192 TEAEs were reported in 50 participants (30.7%) treated with POS alone, and 30 TEAEs were reported in 12 participants (15.0%) treated with POS in Stage 2. In participants treated with placebo + LDP, 41 TEAEs were reported in 18 participants (22.2%). The POS + LDP arm had 2 TEAEs (mild conjunctival hyperemia and mild eye irritation) leading both to study medication discontinuation and withdrawal from the study. No participants had any serious TEAEs, and no participants died during the study. Three participants withdrew from the study due to a TEAE. All 3 events were related to Coronavirus Disease 2019 (COVID-19). There were no SAEs or deaths during the study. The only AEs occurring in ≥ 5% of participants were instillation site irritation and conjunctival hyperemia.

4 OBJECTIVES AND PURPOSE

The VEGA-3 study is a randomized, double-masked, placebo-controlled, multicenter study of the safety and efficacy of POS in participants with presbyopia.

The primary objective of this study is:

- To evaluate the efficacy of POS to improve DCNVA without loss of BCDVA compared to placebo in participants with presbyopia

Secondary objectives of this study are:

- To evaluate additional efficacy measures, such as VA and PD, across multiple time points and visits for POS in participants with presbyopia
- To evaluate tachyphylaxis of the DCNVA response to POS after 6 weeks of dosing
- To evaluate the effect of iris color, baseline PD, and baseline DCNVA on the efficacy of POS in participants with presbyopia
- To evaluate the ocular and systemic safety of POS in participants with presbyopia
- To evaluate participant-reported outcomes of POS in participants with presbyopia

5 STUDY DESIGN

This is a randomized, double-masked, placebo-controlled, multicenter, Phase 3 study in approximately 545 participants with presbyopia.

On Day -7 to -1 (Screening), participants will be assessed for eligibility.

On Day 1 (Baseline), participants will be reassessed for all VA measurements and, if eligibility is met, will be randomized 3:2 to 1 of 2 treatment arms:

- Daily evening POS (n=327)
- Daily evening placebo (ie, POS vehicle; n=218)

Randomization will be stratified by iris color (light/dark irides; Appendix 1).

The study eye is defined as the eligible eye with the worse baseline DCNVA at Visit 2 (Day 1; Baseline). If both eyes have the same baseline DCNVA, then the eye with the better BCDVA will be the study eye. If both DCNVA and BCDVA are equivalent between eyes, the study eye will be the right eye. The study eye and fellow eye will both be evaluated with all assessments. For all assessments other than VA, the baseline values will be determined during screening assessments at Visit 1. For PD and VA measurements, assessments at Visit 2 will be used to determine baseline values.

Study medication will be administered as a single drop in each eye by site staff on Day 1 (Visit 2; Baseline). Starting Day 2, study medication will be self-administered by the participant for approximately 48 weeks as a single drop in each eye in the evening near bedtime. On the evening prior to each office visit, participants should dose as close as possible to 12 hours prior to the scheduled time for each office visit (Visits 3 through 12).

5.1 Primary Endpoint

The primary efficacy endpoint is the percentage of participants with ≥ 15 letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Visit 4 (Day 8).

This comparison will be analyzed first using a hierarchical testing method.

5.2 Secondary Endpoints

Secondary efficacy endpoints will include the following:

- Percentage of participants with ≥ 15 letters of improvement in binocular **DCNVA** and with < 5 letters of loss in binocular **BCDVA** from baseline (excluding primary outcome time point)
- Percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement in **DCNVA** from baseline (monocular and binocular)
- Change in **DCNVA** from baseline (monocular and binocular)
- Change in mean binocular **DCNVA** from baseline at Week 6 compared to the best prior observed change from baseline in mean binocular **DCNVA** in participants treated with POS

- Percentage of participants with **DCNVA** ≤ 20/15, ≤ 20/20, ≤ 20/25, ≤ 20/32, ≤ 20/40, ≤ 20/50, ≤ 20/63, ≤ 20/80, ≤ 20/100, ≤ 20/125, and ≤ 20/160
- Percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement in binocular distance-corrected intermediate visual acuity **(DCIVA)** from baseline
- Change in binocular **DCIVA** from baseline
- Percentage of participants with loss or improvement in **BCDVA** from baseline (monocular and binocular)
- Change in **BCDVA** from baseline (monocular and binocular)
- Change and percent change in **PD** from baseline
- Percentage of participants with **PD** of < 3.5, < 3.0, < 2.5, < 2.0, and < 1.5 mm
- Percentage of participants with **PD** of 1.5 to < 2.0 mm, 2.0 to < 2.5 mm, 2.5 to < 3.0 mm, and 3.0 to < 3.5 mm
- Percentage of participants with baseline **DCNVA** ≤ 20/63, ≤ 20/80, ≤ 20/100, ≤ 20/125, and ≤ 20/160, with a ≥ 10-letter and ≥ 15-letter improvement in **DCNVA**
- Percentage of participants with baseline **DCNVA** from 20/50 to 20/63, 20/50 to 20/80, 20/50 to 20/100, 20/50 to 20/125, and 20/50 to 20/160, with a ≥ 10-letter and ≥ 15-letter improvement in **DCNVA**
- Change from baseline in overall and component participant-reported outcomes

[redacted]

Secondary safety and tolerability endpoints measured at all office visits (Table 1) will include the following:

- Adverse events
- Intraocular pressure (IOP)

- Best-corrected distance VA
- Slit lamp biomicroscopy
- Automated corneal specular microscopy (at select sites)
- Undilated ophthalmoscopy
- Vital signs (HR and BP)
- Urine pregnancy test (for females of childbearing potential)

[redacted]

- [redacted]
- [redacted]

5.3 Description and Schedule of Visits and Procedures

Approximately 545 participants will be randomized in a 3:2 ratio to 1 of 2 treatment arms (POS or placebo). Randomization will be stratified by iris color (light/dark irides). Study procedures are shown in detail in Table 1.

Table 1 Visit Schedule and Assessments

Visit	1	2			3	4	5	6	7	8	9	10	11	12
	Screening	Baseline Day 1			Day 3	Day 8	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 42	Week 48/EOS
Window	Day -7 to -1	N/A			N/A	± 1 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d
Time		0	0.5	1										
Informed consent	X													
Participant ID # assigned	X													
Medical/Ophthalmic history	X													
Demographics	X													
Prior/Concomitant medications [a]	X	X			X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [b]	X	X						X		X		X		X
HR/BP [c]	X					X	X	X	X	X	X	X	X	X
Manifest refraction and near add	X					X		X		X		X		X
PD (photopic) [d]	X	X			X	X								
DCNVA (photopic) [e]	X	X [k]	X	X	X	X	X							
DCIVA (photopic) [e]	X	X		X	X	X	X							
BCDVA (photopic) [e]	X	X [k]		X	X	X	X	X	X	X	X	X	X	X
Best-corrected near VA (photopic)	X	X [k]												
Slit lamp biomicroscopy	X				X	X	X	X	X	X	X	X	X	X
Automated corneal specular microscopy [f]	X				X	X		X		X		X		X
TBUT and CFS [g]	X													
IOP [h]	X				X	X		X		X		X		X
Ophthalmoscopy [i]	X				X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization [j]		X												
Participant questionnaire		X			X	X	X							
In-office treatment: POS or placebo		X												
Treatment/Participant diary dispensing [l]				X			X	X	X	X	X	X	X	
Return of study medication [m]							X	X	X	X	X	X	X	X

AE, adverse event; BCDVA, best-corrected distance visual acuity; BP, blood pressure; CFS, corneal fluorescein staining; D, diopter; DCIVA, distance-corrected intermediate visual acuity; DCNVA, distance-corrected near visual acuity; EOS, End of Study; HR, heart rate; IOP, intraocular pressure; N/A, not applicable; PD, pupil diameter; POS, phentolamine ophthalmic solution; TBUT, tear break-up time; VA, visual acuity.
[a] This includes asking if participants have been diagnosed with dry eye, take prescription drops for dry eye, or take artificial tear drops routinely for dry eye. Investigators will note changes to concomitant medications at any time throughout the study.
[b] Urine pregnancy test is for females of childbearing potential only.
[c] HR and BP can be measured manually or with available digital devices.
[d] PD will be measured using a NeurOptics VIP-300 or VIP-400 pupillometer (mm).
[e] Binocular VA assessments will be conducted first, followed by assessment of each eye individually at Screening; thereafter, study eye will be assessed first, followed by fellow eye and then binocular.
[f] Automated corneal specular microscopy will be performed at select sites only.
[g] Dry eye test will include both TBUT (performed first) and CFS.
[h] IOP will be assessed using Tono-Pen or Goldmann applanation tonometry.
[i] Direct or indirect ophthalmoscopy will be performed without dilation. Use of 90 D lens (indirect) is allowed.
[j] A randomization number is assigned after the participant is qualified.
[k] Participants must requalify for inclusion criteria #5, #6, and #7 at Baseline Time 0 min to be eligible for the study.
[l] All participants will be reminded to instill treatment approximately 12 hours prior to the scheduled time of their next office visit.
[m] Participants should return both used (empty) and unused vials.

5.3.1 Visit 1 (Screening)/Day -7 to -1

Potential participants are identified by the study center to schedule the Screening Visit. Contact lenses, if worm by the participants, should be removed at least 1 hour prior to the first ophthalmic assessment.

The start of Screening includes an explanation of the study and signing of the informed consent form (ICF), assigning a participant ID #, a medical and ophthalmic history, demographics, prior medications review, urine pregnancy test (for females of childbearing potential only), HR and BP, and eligibility assessments.

Participants will be assessed in each eye for manifest refraction and near add, BCDVA, DCNVA, DCIVA, best-corrected near VA, and PD (inclusion criteria #5–8) and automated corneal specular microscopy (at select sites).

Participants must meet all inclusion criteria (including each eye of the participant meeting inclusion criteria #5, #6, #7, and #8) and must not meet any exclusion criteria to be eligible for enrollment.

Before further screening criteria are evaluated, slit lamp biomicroscopy will be performed to establish baseline values.

Final screening must include baseline tear break-up time (TBUT), corneal fluorescein staining (CFS), IOP measurement (using a Tono-Pen or Goldmann applanation tonometry), and undilated ophthalmoscopy.

5.3.2 Visit 2 (Baseline)/Day 1

Participants passing all eligibility criteria at Visit (Screening) will be assessed for prior medications review, urine pregnancy test (for females of childbearing potential only), PD, DCNVA, best-corrected near VA, DCIVA, BCDVA, and AEs at Time 0 min of the Baseline Visit/Day 1 and if the participants meet inclusion criteria #5, #6, and #7 at this visit, they will then be randomized into the study. The first dose of study medication will be administered at the study site by site staff at the Baseline Visit/Day 1 and DCNVA and AE assessments will be made at 0.5 and 1 hour post-dose; additionally, DCIVA, BCDVA, and AE assessments will be made at 1 hour post-dose. The participant questionnaire will be administered (Appendix 2). Study treatment and the participant diary will be dispensed.

The first dose of at-home study medication will be administered by participants as 1 drop in both eyes (OU) on Day 2 in the evening near bedtime.

5.3.3 Visit 3/Day 3

During the Day 3 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Photopic PD

Photopic DCNVA

Photopic DCIVA

Photopic BCDVA

Slit lamp biomicroscopy

Automated corneal specular microscopy (at select sites)

Intraocular pressure

Ophthalmoscopy

Adverse events

Participant questionnaire (Appendix 3)

5.3.4 Visit 4/Day 8 ± 1 day

During the Day 8 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Heart rate/BP

Manifest refraction and near add

Photopic PD

Photopic DCNVA

Photopic DCIVA

Photopic BCDVA

Slit lamp biomicroscopy

Automated corneal specular microscopy (at select sites)

Intraocular pressure

Ophthalmoscopy

Adverse events

Participant questionnaire

5.3.5 Visit 5/Week 6 ± 3 days

During the Week 6 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Heart rate/BP

Photopic DCNVA

Photopic DCIVA

Photopic BCDVA

Slit lamp biomicroscopy

Ophthalmoscopy

Adverse events

Participant questionnaire

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.6 Visit 6/Week 12 ± 3 days

During the Week 12 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Urine pregnancy test (for females of childbearing potential only)

Heart rate/BP

Manifest refraction and near add

Photopic BCDVA

Slit lamp biomicroscopy

Automated corneal specular microscopy (at select sites)

Intraocular pressure

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.7 Visit 7/Week 18 ± 3 days

During the Week 18 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Heart rate/BP

Photopic BCDVA

Slit lamp biomicroscopy

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.8 Visit 8/Week 24 ± 3 days

During the Week 24 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Urine pregnancy test (for females of childbearing potential only)

Heart rate/BP

Manifest refraction and near add

Photopic BCDVA

Slit lamp biomicroscopy

Automated corneal specular microscopy (at select sites)

Intraocular pressure

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.9 Visit 9/Week 30 ± 3 days

During the Week 30 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Heart rate/BP

Photopic BCDVA

Slit lamp biomicroscopy

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.10 Visit 10/Week 36 ± 3 days

During the Week 36 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Urine pregnancy test (for females of childbearing potential only)

Heart rate/BP

Manifest refraction and near add

Photopic BCDVA

Slit lamp biomicroscopy

Automated corneal specular microscopy (at select sites)

Intraocular pressure

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.11 Visit 11/Week 42 ± 3 days

During the Week 42 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Heart rate/BP

Photopic BCDVA

Slit lamp biomicroscopy

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

New study medication and participant diary dispensing

5.3.12 Visit 12 (End of Study)/Week 48 ± 3 days

During the Week 48 Visit, the following safety and efficacy measurements will be made approximately 12 hours after the dose of study medication (Time 0 min):

Concomitant medications

Urine pregnancy test (for females of childbearing potential only)

Heart rate/BP

Manifest refraction and near add

Photopic BCDVA

Slit lamp biomicroscopy

Automated corneal specular microscopy (at select sites)

Intraocular pressure

Ophthalmoscopy

Adverse events

Study medication return (used and unused vials)

5.3.13 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the specific visits requested in the protocol as possibly required for the participant's ophthalmic condition. The Investigator will perform all procedures necessary to evaluate the participant at these visits and record any AEs in the electronic Case Report Form (eCRF).

As noted in Section 5.10.4, every possible effort should be made by Investigators to assure that participants who discontinue early from the study have a follow-up telephone call that includes assessments of AEs and concomitant medications.

5.3.14 Visit Variation

The Day 8 Visit may occur with a window of ± 1 day, and all subsequent visits may occur with a window of ± 3 days.

5.4 Measures Taken to Minimize/Avoid Bias

This is a randomized, placebo-controlled, double-masked, Phase 3 study. The placebo ophthalmic solution and the POS ophthalmic solution will be provided in identical packaging to ensure masking to Investigators, site staff, study participants, the contract research organization (CRO), and Ocuphire.

5.5 Study Medications

Study Medication Identification

The POS study medication is phentolamine mesylate; its chemical name is 3-[N-(4,5-dihydro-1H-imidazol-2-ylmethyl)-4-methylanilino]phenol;methanesulfonic acid. It is a white to off-white, odorless crystalline powder with a molecular weight of 377.46 g/mol. Solutions of phentolamine mesylate are acid to litmus. It is freely soluble in water and in ethanol and slightly soluble in chloroform. It melts at approximately 178ºC.

5.5.1 Packaging and Labeling

The investigational products, POS and placebo, are packaged in a 0.5-mL low-density polyethylene Blow-Fill-Seal vial containing 0.3 mL solution for single-dose use. Five individual vials are included in a molded strip. Each strip containing 5 vials is wrapped with a multicolor "rainbow" aluminum foil overwrap that has been purged with nitrogen. The foil is impermeable to water and oxygen and will be labeled with an investigational label showing the study protocol number and other relevant information, including a statement "Caution – New Drug – Limited by Federal (United States [US]) Law to Investigational Use."

5.5.2 Storage of Study Medication and Dispensing

Prior to dispensing, all investigational material must be stored in a secure location with strictly limited access documented by signature of authorized persons who may dispense investigational materials.

Study medication (POS and its placebo) should be shipped and stored at the study site refrigerated (2°C to 8°C, 36°F to 46°F) until provided to the participant, and then the participant can store it at room temperature (15°C to 25°C, 59°F to 77°F). Study medication must not be frozen and must be protected from light.

5.5.3 Study Medication Administration

Study medication will be dispensed by the Investigator or designee at the site at Visit 2 (Baseline). If the participant wears contact lenses, they must be removed prior to dosing and not replaced until the next morning at the earliest.

The participant will instill 1 drop of study medication QD OU from the same vial in the evening near bedtime for approximately 48 weeks (± 3 days) beginning the evening of Day 2. On the evening before each of the remaining visits (Day 8 and Weeks 6, 12, 18, 24, 30, 36, 42, and 48), participants should dose study medication as close as possible to 12 hours prior to the scheduled time for those visits.

5.5.4 Study Medication Accountability

5.5.4.1 Receipt and Disposition of Study Medication

The Investigator or designee (eg, Study Coordinator or Pharmacist) will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study medication using the inventories supplied by Ocuphire and for monitoring dosing compliance using participant diaries. The Study Monitor will review dispensing and study medication accountability records during site visits and at the completion of the study and note any discrepancies.

Each participant will receive sufficient study medication for approximately the next 6 weeks; thus, participants will receive additional study medication at the Week 6, 12, 18, 24, 30, 36, and 42 Visits. A study medication kit will be dispensed at Visit 2 (Baseline; Day 1). As described in Section 7.1, the participant will empty any remaining contents from the single-use vial following each instillation. The participant should then place the vial in the study medication kit for return to the study site. All opened vials and any unopened study medication will be returned at Visits 5 through 12.

5.5.4.2 Return of Study Medication by Study Site

When the study is completed or is terminated by Ocuphire, all study materials, including used and unused study medication vials, must be returned to Ocuphire (or its designee) or destroyed under the direction of the same. All study medication accounting procedures must be performed before the study is considered completed. A final study medication disposition will be completed by the Study Coordinator.

5.6 Expected Duration of Participant Participation

The length of participant participation is approximately 48 weeks, with 12 clinic visits summarized below:

- Visit 1 (Screening)/Day -7 to -1
- Visit 2 (Baseline)/Day 1
- Visit 3/Day 3
- Visit 4/Day 8 (± 1 day)
- Visit 5/Week 6 (± 3 days)
- Visit 6/Week 12 (± 3 days)
- Visit 7/Week 18 (± 3 days)
- Visit 8/Week 24 (± 3 days)
- Visit 9/Week 30 (± 3 days)
- Visit 10/Week 36 (± 3 days)
- Visit 11/Week 42 (± 3 days)
- Visit 12 (End of Study)/Week 48 (± 3 days)

5.7 Randomization and Procedure for Breaking the Code

A randomization code for allocating participants to each treatment arm will be prepared by a masked biostatistician not connected with the study. participants will be stratified by iris color (light/dark irides).

At the initiation of study-related procedures, every participant screened is assigned a participant number within numerical order within each site. Once a participant is qualified for the study, the participant is assigned a ***randomization number*** in the order provided by the biostatistician.

Study medications will be masked to Investigators, site staff, study participants, the CRO, and Ocuphire. Only in case of medical emergency or occurrence of SAEs will the randomization code be unmasked by the Medical Monitor and made available to the Investigator, Ocuphire, and/or other personnel involved in the monitoring or conduct of this study.

5.8 Collection of Data

Study-specific data that have been outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator. Data will be verified electronically using a series of online programmed edit checks that have been created by the Clinical Data Manager and programmed by the Clinical Data Programmer or designee. Data discrepancies will be brought to the attention of the clinical team and investigated by the Study Monitor and site staff. Study Monitors will review and verify all data collected in the eCRF against any applicable source documentation during remote review or scheduled monitoring visits. The Study Monitor will work closely with the site staff to address any discrepancies found so that proper resolutions can be made and documented in the clinical database. An audit trail within the system will track all changes made to the data.

5.9 Completed Participant

A completed participant is defined as one who completes all planned procedures through the end of Visit 12 (End of Study)/Week 48.

5.10 Non-Completing Participant

A non-completing participant is defined as one who exits the study by their own volition or at the discretion of the Investigator and/or the Medical Monitor prior to completing all of the study procedures required in this protocol. Any participant may decide to voluntarily withdraw from the study at any time without prejudice.

5.10.1 Study Medication Discontinuation

Study medication may be discontinued for the following reasons:

- **Adverse event:** Adverse events include clinically significant laboratory abnormalities and intercurrent diseases reported by the participant or observed by the Investigator, with documentation on the eCRF
- **Death:** If a participant dies, the AE(s) that caused the death should be documented on the eCRF and be noted as serious and fatal
- **Disallowed concurrent medication:** Any medication not allowed by the protocol would be a protocol violation
- **Lack of efficacy:** A participant may elect to discontinue participation in the study for a perceived lack of efficacy
- **Investigator decision:** A participant may be discontinued for reasons other than those bulleted previously if the Investigator thinks it is not in the best interest of the participant to continue
- **Other:** If there is any other reason for participant discontinuation, this should be documented on the eCRF

5.10.2 Reasons for Withdrawal From Study

- Participant withdraws consent
- Participant withdraws due to an AE

- Participant is lost to follow-up
- Participant withdraws for other reason

5.10.3 Entire Study Terminated

The entire study may be terminated by Investigators or Ocuphire. Prompt, written notice of reasonable cause to the other party (Ocuphire or Investigators, respectively) is required. Prompt notice to the Institutional Review Board (IRB) and to regulatory authorities is also required.

5.10.4 Actions After Discontinuation

All participants who discontinue study medication due to a report of an AE **must** be followed up and provided appropriate medical care until their signs and symptoms have remitted or stabilized or until medical assessments have returned to acceptable or pre-study limits.

For any participant who chooses to withdraw consent or who is noncompliant, every possible effort should be made by the Investigator to assure the Visit 4/Day 8 DCNVA, BCDVA, and other measurements are assessed prior to discontinuation, in addition to a follow-up telephone call that includes assessments for AEs and concomitant medications.

5.11 Completed Study

The study is completed when all randomized participants have completed or discontinued the study, all eCRFs have been completed, and all data have been entered into the database. Final database lock will occur after the last randomized participant completes the last visit, all data have been entered, and all queries are resolved.

6 PARTICIPANT INCLUSION AND EXCLUSION CRITERIA

6.1 Participant Inclusion Criteria

Participants must meet all of the following criteria:

1. Males or females ≥ 45 and ≤ 64 years of age
2. Able to comply with all protocol-mandated procedures independently and to attend all scheduled office visits
3. Able and willing to give signed informed consent
4. Able to self-administer study medication throughout the study period

Inclusion criteria #5, #6, and #7 must all be met at both Screening and Baseline Visits:

5. Best-corrected distance VA of 55 ETDRS letters (20/20 Snellen equivalent) or better in photopic conditions in each eye
6. Distance-corrected near VA of 50 ETDRS letters (20/50 Snellen equivalent) or worse but not <35 ETDRS letters (20/100 Snellen equivalent) in photopic conditions in each eye and binocularly
7. For participants who depend on reading glasses or bifocals, binocular best-corrected near VA of 65 ETDRS letters (20/25 Snellen equivalent) or better
8. Photopic PD of ≥ 4 mm in the study eye at Screening

6.2 Participant Exclusion Criteria

Excluded from the study will be individuals with any of the following characteristics:

Ophthalmic (in either eye):

1. Use of any topical prescription (including Vuity® or Qlosi™) or over-the-counter (OTC) ophthalmic medications of any kind within 7 days of Screening until study completion, with the exception of lid scrubs with OTC products (eg, OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.) and artificial tears as specified in Exclusion Criterion #2 below
2. Use of any OTC artificial tears (preserved or unpreserved) during visit days or 15 min before or after instillation of study medication
3. Use of Ryzumvi™ (POS) within 7 days prior to Screening
4. Use of any dry eye product, such as topical ophthalmic therapy for dry eye (eg, generic cyclosporine, Restasis®, Xiidra®, Cequa®, Eysuvis®, and Meibo®) or intranasal dry eye product (eg, Tyrvaya®) or other devices within 12 months prior to Screening
5. Tear break-up time of < 5 seconds or CFS Grade ≥ 2 in the inferior zone or Grade ≥ 1 in the central zone using the National Eye Institute scale
6. Clinically significant ocular disease (eg, cataract, glaucoma, corneal edema, uveitis, retinal degeneration, loss of visual field, or any macular pathology) that, in the judgment of the Investigator, might interfere with study procedures

7. Recent or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, keratitis, etc.). Participants must be symptom free for at least 7 days prior to Screening
8. Any history of herpes simplex or herpes zoster keratitis
9. Known allergy, hypersensitivity, or contraindication to any component of the phentolamine or vehicle formulations
10. Prior participation in a study involving the use of POS for the treatment of presbyopia or night vision disturbance
11. History of cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal
12. Ocular trauma within 6 months prior to Screening
13. Ocular surgery or any ocular laser treatment within 6 months prior to Screening. Any history of radial keratotomy is prohibited
14. Participants with surgical monovision, multifocal, or extended depth-of-focus IOLs. Monofocal IOLs are acceptable if in place > 6 months prior to Screening
15. Monofocal IOL in place > 6 months prior to Screening with any posterior capsule opacification
16. History of any traumatic (surgical or nonsurgical) or nontraumatic condition affecting the pupil or iris (eg, irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy, iridectomy, iritis, etc.)
17. Unwilling or unable to discontinue use of contact lenses at least 1 hour prior to Screening for soft contact lenses or at least 8 hours prior to Screening for hard gas permeable contact lenses, and at least 8 hours (for both types of lenses) prior to all other office visits

Systemic:

18. Known hypersensitivity or contraindication to alpha- and/or beta-adrenoceptor antagonists (eg, chronic obstructive pulmonary disease or bronchial asthma; abnormally low BP or HR; second- or third-degree heart blockage or congestive heart failure)
19. Known hypersensitivity or contraindication to any systemic cholinergic parasympathomimetic agent
20. Clinically significant systemic disease (eg, uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere with the study as deemed by the judgment of the Investigator
21. Initiation of treatment with, or any changes to, the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs within 7 days prior to Screening or during the study; however, Flomax® (tamsulosin) is specifically excluded
22. Participation in any investigational study within 30 days prior to Screening
23. Females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods

include the use of at least one of the following: intrauterine device, hormonal contraception (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. A female is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post–surgical sterilization. All females of childbearing potential, including those with post−tubal ligation, must have a negative urine pregnancy test result at Visit 1 (Screening)

24. Resting HR outside the range of 50 to 110 beats per min (bpm) following at least a 5-min rest period in the sitting position at Visit 1 (Screening). Heart rate may be repeated **only once** if outside the specified range, following another 5-min rest period in the sitting position
25. Hypertension with resting diastolic BP > 105 mmHg or systolic BP > 160 mmHg following at least a 5-min rest period in the sitting position at Visit 1 (Screening). Blood pressure may be repeated **only once** if outside the specified range, following another 5-min rest period in the sitting position

7 TREATMENT OF PARTICIPANTS

Approximately 545 participants will be randomized in a 3:2 ratio to 1 of 2 treatment arms (POS or placebo). Randomization will be stratified by iris color (light/dark irides).

7.1 Treatment Adherence

All participants must be instructed on the importance of following the QD regimen and maintaining their dosing diaries. At Visit 2 (Baseline)/Day 1, participants will receive 1 drop of study medication OU instilled by site staff. On Day 2, participants will initiate self-administration of 1 drop of study medication OU in the evening near bedtime. Participants will repeat this instillation, using 1 vial per day, for a total of 48 weeks over the course of the study. Participants are to empty any remaining contents from the single-use vial following each instillation and bring all empty, opened vials as well as any unopened study medication in the study medication kit to the study site at Visit 5/Week 6 and at each visit thereafter. Treatment adherence will be measured by counting the vials at the start of the study and those remaining at Visit 5/Week 6 and at each visit thereafter. Participants will also bring their diary to each post-baseline visit and dosing will be reviewed by site staff.

7.2 Concomitant Medications

As noted in the exclusion criteria (Section 6.2), use of any topical prescription (including Ryzumvi) or OTC ophthalmic medications of any kind within 7 days prior to Screening is prohibited, with the exception of lid scrubs with OTC products (eg, OCuSOFT lid scrub, SteriLid, baby shampoo, etc.). Many drugs, both prescription and OTC, contain active ingredients that can affect PD. This includes many eye drops such as Visine® that are used to reduce redness, most cough or cold preparations, antihistamines and bronchodilators, most nasal drops, most BP medications, many drugs used for migraines, and many other products. Use of artificial tears is prohibited during visit days or 15 min before or after instillation of study medication. Use of any dry eye product, such as topical ophthalmic therapy for dry eye (eg, generic cyclosporine, Restasis, Xiidra, Cequa, and Eysuvis) or intranasal dry eye product (eg, Tyrvaya) or other devices within 12 months prior to Screening is prohibited.

Additionally, initiation of treatment with or any changes to the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs (Appendix 4) within 7 days prior to Screening or during the study is prohibited. However, a participant can be treated with a systemic adrenoceptor antagonist, for example, as long as the particular agent and its dose and regimen had been consistent for the 7 days prior to Screening, and there is no reason to believe that alteration will be necessary at some point later during the study. Use of Flomax (tamsulosin) is specifically excluded.

If there is any question about whether a medication is acceptable, the Medical Monitor should be consulted before proceeding.

Use of all medications will be documented on the appropriate eCRF. Judgment of continued study participation by the participant and inclusion of this participant's subsequent visits in the safety and efficacy analysis will be made by Ocuphire.

All medications taken by the participant within 30 days prior to Screening and during the study will be documented on the eCRF. The name of the drug, dose, route of

administration, duration of treatment, and indication will be recorded for each medication. For combination products (eg, Contac®, Cosopt®), the brand name is required. For non-combination products, the generic name is desired. The use of routine ophthalmic diagnostic pharmaceutical agents (eg, fluorescein and local anesthetic) will be allowed and should be documented. Any change in dosing parameters should also be recorded in the eCRF.

8 ASSESSMENT OF EFFICACY

8.1 Specification of the Efficacy Parameters

The primary efficacy endpoint is the percentage of participants with ≥ 15 letters of improvement in photopic binocular DCNVA and with < 5 letters of loss in photopic binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Visit 4 (Day 8). Other efficacy endpoints can be found in Section 5.2 and Table 1.

8.2 Assessing, Recording, and Analyzing Efficacy Parameters

Visual acuity, PD, and participant questionnaire (Appendix 2 and Appendix 3) will be measured at visits as described in Section 5.3.

The participant should be in the same room for all assessments, and every effort will be made to have the same staff member perform the measurements at all visits.

The study eye, fellow eye, and binocular measurements will be evaluated at all appropriate assessments. All of the efficacy endpoints will be analyzed overall and by light/dark irides at all time points.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

The assessment of safety and tolerability is a primary objective of this study and will be evaluated by:

- Adverse events
- Intraocular pressure
- Best-corrected distance VA
- Slit-lamp biomicroscopy
- Automated corneal specular microscopy (at select sites)
- Undilated ophthalmoscopy
- Heart rate and BP

Urine pregnancy tests for females of childbearing potential will also be conducted.

9.2 Adverse Events and Serious Adverse Events

All AEs and SAEs that occur following consent and until the final study visit should be collected and recorded on the AE or SAE eCRF page. Only TEAEs/treatment-emergent adverse reactions will be summarized (Section 10.3.7).

All AEs/adverse reactions occurring during the study (ie, once the participant has signed the informed consent) **must** be documented, regardless of the assumption of causal relationship, on the respective eCRF. All TEAEs/adverse reactions must be documented from the time the participant receives the study medication until the participant's participation in the study has been completed. If a participant has ongoing AEs/adverse reactions at the time of study completion or discontinuation from the study, the ongoing AEs/adverse reactions **must** be followed up and provided appropriate medical care until the signs and symptoms have remitted or stabilized or until medical assessments have returned to acceptable or pre-study limits.

Documentation of AEs/adverse reactions includes start date and end date, severity, relationship to study medications, action(s) taken, seriousness, and outcome.

9.2.1 Adverse Event Definitions

The following definitions of terms apply to this section:

Adverse event. An AE is any untoward medical occurrence associated with the use of a study medication in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational product under evaluation and the comparator product or vehicle placebo given or administered during any phase of the study.

Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen after starting the investigational treatment. Abnormal test

results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the participant at each visit during the study. At each clinic assessment/visit, study personnel should ask the following question: “Have you had any problems since your last assessment/visit?”. Adverse events also may be detected when they are volunteered by the participant during or between visits or through study assessments.

Life-threatening AE or life-threatening suspected adverse reaction. An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Ocuphire, its occurrence places the participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious AE or serious suspected adverse reaction. An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Ocuphire, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other medically important serious event

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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that is unrelated to the medication under study and has not worsened since the start of the study is not considered an SAE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Unexpected AE or unexpected suspected adverse reaction. 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 general investigational plan or elsewhere in the current application, 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 as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

The study medication relationship for each AE/adverse reaction should be determined by the Investigator using these explanations:

- Not related
- Unlikely related
- Possibly related
- Probably related
- Definitely related
- Unknown

Unless the relationship is considered to be "Not related" or "Unlikely related" and there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered "related".

Severity of an AE is defined as a qualitative assessment of the level of discomfort of an AE as is determined by the Investigator or reported to him/her by the participant. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

- 1 = Mild: present, but not distressing, and no disruption of normal daily activity
- 2 = Moderate: discomfort sufficient to reduce or affect normal daily activity
- 3 = Severe: incapacitating, with inability to work or perform normal daily activity

A change in severity for a reported AE will require an end date for the previous severity and a new start and end date for the new severity. For example, a change in severity may go from mild to severe or from severe to moderate. In either case, the start or end times/dates should be recorded.

The term "severe" is used to describe the intensity of an event/reaction; the event/reaction itself may be of relatively minor medical significance (such as a severe headache). This is not the same as a "serious" AE, which is based on a participant/event outcome or action criteria usually associated with events that pose a threat to the participant's life or vital functions. "Seriousness" (NOT severity) serves as a guide for defining regulatory reporting obligations.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form and emailed to [redacted], as well as recorded in the eCRF. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

Action taken in response to an AE is coded as:

- Dose increased: An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount
- Dose not changed: An indication that a medication schedule was maintained
- Dose reduced: An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount
- Dose interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication
- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication
- Not applicable: Determination of a value is not relevant in the current context
- Unknown: Not known, not observed, not recorded, or refused

Additional other action taken:

- Concomitant medication
- Hospitalization

Outcome of an AE is coded as:

- Fatal: The termination of life as a result of an AE
- Not recovered/not resolved: One of the possible results of an AE outcome that indicates that the event has not improved or the participant has not recuperated
- Recovered/resolved: One of the possible results of an AE outcome that indicates that the event has improved or the participant has recuperated
- Recovered/resolved with sequelae: One of the possible results of an AE outcome in which the participant recuperated but retained pathological conditions resulting from the prior disease or injury
- Recovering/resolving: One of the possible results of an AE outcome that indicates that the event is improving or the participant is recuperating
- Unknown: Not known, not observed, not recorded, or refused

In previous clinical studies of POS, the most frequently reported AE was conjunctival hyperemia. Investigators are cautioned to use the appropriate verbatim term on the AE form to describe this observation:

- Redness related to instillation that is transient (ie, is no longer present 2 hours after instillation) = “conjunctival erythema upon instillation”

- Redness that is NOT transient (ie, is present ≥ 2 hours after instillation) = "conjunctival hyperemia"

Expedited reporting of serious and unexpected AEs: All SAEs (related and unrelated) will be recorded following participant signature of the informed consent and until Visit 12 (End of Study)/Week 48. Any SAEs "suspected" to be related to the study medication and discovered by the Investigator at any time **after** the study should be reported.

Any SAE that occurs must be reported to the CRO within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to the CRO as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the participant should be maintained at the site with a copy emailed to [redacted] The Investigator must assess the SAE relationship and complete the SAE form. The CRO may request additional information. Follow-up information (eg, discharge summary) will be retained in the participant's chart and a copy will be emailed to [redacted] In addition, all SAEs should be recorded on the AE eCRF page with the serious question marked "Yes".

It is the Investigator's responsibility to notify the approving IRB of any SAEs on a timely basis as instructed by Ocuphire following Ocuphire's determination of causality. All participants who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event. Ocuphire will report all SAEs to the Food and Drug Administration (FDA) on the appropriate schedule depending if the event is drug related or not drug related and expected or unexpected (based on the available information in the IB).

Any death occurring during the study and follow-up period must be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study medication, the SAE resulting in the death must be reported to the CRO. A death occurring after completion of the study that is not reasonably associated with study medication administration does not require completion of the SAE form.

9.2.2 Follow-Up of Participants After Adverse Events

If an AE/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. All AEs ongoing at the time of the last visit or discontinuation from the study will be followed up until the AE/adverse reaction is resolved or stabilized, the participant is lost to follow-up, or there is other resolution to the event.

10 STATISTICS

10.1 Sample Size

Using $\alpha = 0.05$ significance and a two-tailed test, 525 evaluable participants (313 participants each in the POS arm and 212 participants in the placebo arms) who are evaluable for efficacy will provide greater than 90% power to detect a difference of 11.5% between treatments in percentage of participants with ≥ 15 letters of improvement in photopic binocular DCNVA and with < 5 letters of loss in photopic binocular BCDVA from baseline at 12 hours post-dose at Visit 4 (Day 8). [redacted] An additional 20 participants will be enrolled to account for dropouts.

10.2 Analysis Populations

Modified Intention-to-Treat Population (mITT): The mITT Population will include all randomized participants who received at least 1 dose of study medication. The mITT Population will be used for the primary endpoint analysis and to analyze efficacy endpoints, with participants included in their randomized treatment regardless of the treatment they actually received.

Per Protocol Population: The PP Population will include all participants in the mITT Population who received at least 80% of expected doses of study medication through Day 8, have Baseline and Day 8 DCNVA and BCDVA measurements, and have no major protocol deviations considered to have significant impact on treatment outcome. The PP Population will be used to analyze efficacy endpoints, with participants included in their randomized treatment group regardless of the treatment they received.

All Randomized Population (ARP): The ARP will include all randomized participants. This population is also known as the Intention-to-Treat (ITT) Population.

Safety Population: The Safety Population will include all randomized participants who have received at least 1 dose of study medication. The Safety Population will be used to summarize safety variables, using the actual treatment a participant received.

10.3 Statistical Methods

10.3.1 General Considerations

All continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical variables will be summarized by treatment using counts and proportions.

All study data will be listed by treatment group and participant.

All statistical tests will be performed using a significance level of 5% (two-tailed). The p-values for the analysis of secondary efficacy endpoints will be considered descriptive.

10.3.2 Demographic and Baseline Characteristics

Participant demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for the mITT Population, PP Population, Safety Population, and ARP. The demographics consist of age (year), sex, race, ethnicity,

study eye (right or left), and irides type (light or dark). These data will also be provided in by-participant listings.

10.3.3 Participant Disposition

A summary of the analysis sets includes the number and percentage of participants by treatment group and overall for the following categories: participants in the ARP, participants in the Safety Population, participants in the mITT Population, and participants in the PP Population. All percentages will be based on the number of participants in the ARP. End-of-study information will also be summarized in this table, including the number of participants completing Week 6, the number of participants completing the study, the number of participants who prematurely discontinued the study with reasons for withdrawal, and the number of participants who prematurely discontinued the study medication with reasons for study medication discontinuation. These data will also be provided in by-participant listings.

10.3.4 Medical History and Prior/Concomitant Medications

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized for all participants by treatment group and overall. Medical history will be provided in by-participant listings.

Prior medications are defined as any medication that has a start and stop date prior to the day of first exposure to any study medication. The total number of prior medications and the number and percentages of participants with at least 1 prior medication will be summarized by treatment.

The total number of concomitant medications and the number and percentages of participants with at least 1 concomitant medication will be summarized by treatment. All summaries will be performed using the Safety Population.

10.3.5 Estimands for Efficacy

The primary efficacy estimand, corresponding to the primary efficacy endpoint, is defined by the following components:

1. The *population* is restricted to the mITT Population
2. The *variable* for the primary endpoint is percent of participants with ≥ 15 ETDRS letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Day 8
3. The *intercurrent events* of treatment discontinuation or use of prohibited concomitant medications will be handled according to the treatment policy strategy, irrespective of premature discontinuation of randomized treatment
4. The *population-level summary* is the difference in percent of participants with ≥ 15 ETDRS letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Day 8, analyzed using a logistic regression model with treatment and light/dark irides as factors and the baseline DCNVA as a covariate
5. *Treatment:* There will be 1 active treatment arm (POS) and 1 control arm (placebo)

Secondary efficacy estimands will have the same population, intercurrent events, and treatment as the primary estimand. For secondary categorical endpoints, the population-level summary will also match the primary estimand; only changes to the variable (eg, visit, type of assessment) will be required to match the particular secondary endpoint.

Secondary efficacy estimands for continuous endpoints will also vary depending on the assessment, visit, and time point. For change from baseline endpoints, the population-level summary is the change from Baseline in the assessment at the required visit, analyzed using analysis of covariance (ANCOVA) with treatment and light/dark irides as factors and the baseline assessment as a covariate.

The following is an example of a secondary efficacy estimand with a change from baseline endpoint:

1. The *population* is restricted to the mITT Population
2. The *variable is* change from baseline in binocular DCNVA at Day 8
3. The *intercurrent event* of treatment discontinuation or use of prohibited concomitant medications will be handled according to the treatment policy strategy, irrespective of premature discontinuation of randomized treatment
4. The *population-level summary* is the change from baseline in binocular DCNVA at Day 8, analyzed using ANCOVA with treatment and light/dark irides as factors and the baseline DCNVA as a covariate
5. *Treatment:* There will be 1 active treatment arm (POS) and 1 control arm (placebo)

10.3.6 Analysis of Efficacy

Unless otherwise noted, efficacy will be assessed using the mITT Population, with participants included in the treatment arm into which they were randomized. Selected analyses will be performed on the PP Population as specified in the Statistical Analysis Plan (SAP).

For the analysis of the primary efficacy endpoint, imputation will be performed for missing observations if applicable; details will be provided in the SAP. If the analysis using the mITT Population shows a positive effect for POS at the 0.05 level of significance, the primary endpoint will be considered met. The primary efficacy endpoint will be analyzed as described in the definition of the primary efficacy estimand. The percentage of participants in each treatment arm meeting the criteria for the primary efficacy endpoint, the difference in proportions with 95% confidence interval (CI), and p-value will be provided.

In addition, the primary efficacy endpoint will be analyzed by light/dark irides using the same model indicated above but without irides as a factor. For these subgroup analyses, observed case data only will be used; that is, missing values will not be imputed. The primary efficacy endpoint will also be analyzed by subgroups based on age, gender, race, and ethnicity; full details will be presented in the SAP.

For all efficacy endpoints, baseline values are defined as the assessment values on Visit 2/Day 1 (pre-dose, if applicable).

Other efficacy endpoints are indicated in Section 5.2 and Table 1.

Each of the continuous secondary efficacy endpoints will be analyzed using ANCOVA with change from baseline as the dependent variable, treatment and light/dark irides as factors, and the respective baseline value included as the covariate. The output from each ANCOVA will include the least-squares (LS) mean and standard error for both treatment arms, along with the placebo-corrected LS mean, its 95% CI, and associated p-value.

For each of the secondary endpoints related to percent of participants achieving certain criteria, the analysis will be performed using a logistic regression model with treatment and light/dark irides as factors and the baseline DCNVA as a covariate. For each analysis, the percentage of participants in each treatment arm meeting the criteria, the odds ratio with 95% CI, and p-value will be provided.

In addition, each secondary efficacy endpoint will be analyzed by light/dark irides using the same model indicated above but without irides as a factor.

Separate analyses will be performed for binocular, study eye, and fellow eye, where applicable.

Tachyphylaxis will be assessed for mean binocular DCNVA by comparing change from Baseline at Week 6 in the POS group to the best change from baseline achieved prior to Week 6 for binocular DCNVA.

A hierarchical analysis will be used to evaluate primary and secondary efficacy endpoints to ensure that the family of tests in the hierarchy will simultaneously be tested at the 0.05 level of significance. A subset of the secondary pairwise comparisons will be included in the hierarchical analysis as specified in the SAP.

Questions from the participant questionnaire will be summarized categorically for each treatment group and visit.

10.3.7 Analysis of Safety

Safety will be assessed using the Safety Population, with participants included in the treatment arm they actually received, regardless of their randomized treatment. Observed case data will be used; no imputation will be performed for missing safety data.

Descriptive statistics of observed values will be presented for vital sign data at each visit including systolic BP (mmHg), diastolic BP (mmHg), and HR (bpm) by treatment group and overall. Changes from baseline (Day 1) to each scheduled post-baseline time point will be presented.

Observed values and change from baseline in IOP will be summarized descriptively using counts and percentages for each treatment group at each visit for the observed value and change from baseline (Day 1). Separate summaries will be created for the study eye, the fellow eye, and the best of either eye.

Verbatim descriptions of AEs will be coded using MedDRA. Only TEAEs (those that occur after the first dose of study medication *or increasing in severity after initiation of study medication*) will be summarized. Treatment-emergent AEs and SAEs will be summarized by treatment, system organ class (SOC) and preferred term, severity, and relationship to study medication. Deaths, withdrawal from study medication due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment. Note that in MedDRA, ocular events are coded to the SOC of “special senses”. Thus, using SOC in the summaries will provide a separation of ocular and non-ocular AEs.

All safety data will be provided in by-participant listings.

10.4 Interim Analyses

The primary efficacy analysis of study data will be conducted after all participants complete Week 6 of the study. All efficacy and safety endpoints through Week 6, as well as the endpoint for tachyphylaxis, will be analyzed. Another interim analysis of safety endpoints will be conducted after all participants complete Month 6 of the study.

For the interim analyses, Sponsor personnel who have access to individual treatment assignments will be kept to a minimum. In particular, Investigators and investigational site staff will remain masked to individual treatment assignments until database lock for final analysis.

10.5 Procedure for Accounting for Missing, Unused, or Spurious Data

For the analysis of the primary efficacy endpoint, imputation will be performed for missing data; details of the imputation, if performed, will be included in the SAP. For the analysis of the other efficacy endpoints, only observed case data will be used. For the summarization of safety data, only observed case data will be used.

10.6 Procedure for Reporting Deviations From the Statistical Plan

Any deviations from the SAP will be described and a justification given in the final Clinical Study Report.

11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The Investigator will permit study-related monitoring visits, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents.

12 QUALITY CONTROL AND QUALITY ASSURANCE

The progress of the study will be monitored by onsite, written, and telephone communications between personnel at the Investigator's site and the Medical Monitor. If any public health concerns restrict Study Monitors from traveling to a site, remote review will be conducted to the extent possible, while still ensuring the study is monitored appropriately per applicable regulations and guidelines. The Investigator will allow Ocuphire, the Study Monitor, and the Medical Monitor to inspect all eCRFs, participant records (source documents), signed ICFs, and records of study medication receipt, storage, preparation, disposition, and regulatory files related to this study.

13 ETHICAL CONSIDERATIONS AND GOOD CLINICAL PRACTICE COMPLIANCE

13.1 Good Clinical Practice Compliance

The proposed study is participant to all applicable governmental rules and regulations concerning the conduct of clinical trials on human participants. This includes, but is not necessarily limited to, the approval of IRBs, the Helsinki Declaration, US FDA law, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, obtaining prospective informed consent, monitoring of the conduct of the study and the completeness of the eCRFs by Ocuphire or its designee(s), and appropriate record retention by the Investigator.

13.2 Institutional Review Board

This protocol, materials used to recruit participants, and materials used to document consent must be approved by the IRB prior to initiation of the study. Written IRB approval must adequately identify the protocol and informed consent. In addition to approving the protocol, the IRB must also approve the participant information and ICF, as well as any advertising tools that will be used for the study. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to Ocuphire, *prior* to the start of participant enrollment into the study.

13.3 Protocol Deviations/Violations

The Investigator should not deviate from the requirements of this protocol without prior written approval of the Medical Monitor or Sponsor, except in the event of a medical emergency.

A reportable protocol deviation is defined as nonadherence to the protocol that involves inclusion/exclusion criteria; affects participant safety, rights, or welfare; or has the potential to affect the integrity of the data. Examples of major protocol deviations include study enrollment by ineligible participant, loss of key data such as equipment malfunction (eg, pupillometer), and/or use of a prohibited medication during the study.

All protocol deviations will be reported by entering the event in the appropriate eCRF page. Protocol deviations should be reported to the IRB in accordance with IRB-specific guidelines. If there is any question as to whether the deviation is reportable, Ocuphire or its designee and the IRB should be contacted.

All changes to the protocol will be made by the Sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

Changes implemented without prior approval will be considered protocol violations.

13.4 Informed Consent Requirements

Written informed consent will be obtained from each participant. A copy of the signed and dated consent document will be given to each participant. The original signed and dated ICF must be maintained in the study files at the Investigator’s site.

The Investigator is responsible for ensuring that no participant is subject to any study-related examination or activity before that participant has given informed consent. The participant must give written consent after the receipt of detailed information. The verbal

explanation will cover all the elements specified in the written information provided for the participant.

It should be emphasized that the participant is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the participant is otherwise entitled. Participants who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact their subsequent care.

The Investigator will inform the participant of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The participant must be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the participant may be given time to reflect, if this is required, or if the participant requests more time. Participants who wish to participate in the study will be required to sign and date the ICF.

A copy of the signed and dated ICF will be given to each participant. The original signed and dated ICF must be maintained in the study files at the Investigator's site. Signed informed consent must be obtained prior to the conductance of any study procedures.

14 DATA HANDLING AND RECORD KEEPING

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and US FDA guidelines for the handling and analysis of data for clinical trials.

14.1 Data Entry

Study-specific data that have been outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator.

14.2 Data Quality Control and Reporting

Data are verified electronically using a series of programmed edit checks that have been created by the Clinical Data Manager and programmed by the Clinical Data Programmer or designee. Data discrepancies will be brought to the attention of the clinical team and investigated by the Clinical Research Associate (CRA) and site staff. Clinical Research Associates will review and verify all data collected in the eCRF against source documentation during scheduled monitoring visits. The CRA will work closely with the site staff to address any discrepancies that have been found so that proper resolutions can be made and documented in the clinical database. An audit trail within the system will track all changes made to the data.

14.3 Archiving of Data

Archived versions of the database will be saved by Ocuphire consistent with ICH GCP guidelines, complying with whichever of the requirements is longer. Ocuphire will notify the Investigator when documents should be returned.

14.4 Records Retention

The Investigator’s site and clinical laboratory will retain all records related to the study in compliance with ICH GCP guidelines.

14.5 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from or change to the protocol without discussion with and agreement by Ocuphire and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study participants or where the change(s) involves only logistical or administrative aspects of the study (eg, change in Study Monitor, change of telephone number).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

15 SUMMARY OF CHANGES

Bold underlined text shows additions; strikethrough text shows deletions. For changes that affect multiple sections of the protocol, the change is listed once at the first instance in the table below, and each subsequent protocol section incorporating that change is also listed at that point. Any administrative or minor editing changes not affecting the content or conduct of the protocol that have been made are not listed.

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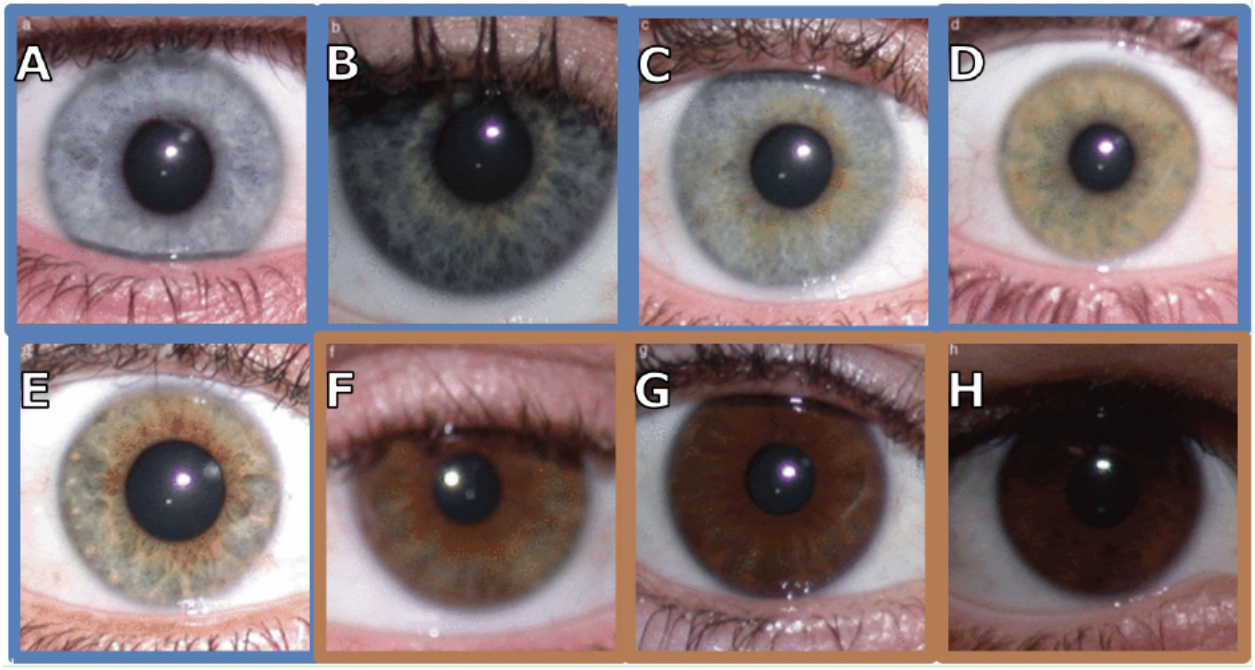
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16 BIBLIOGRAPHY

1. American Optometric Association. Adult Vision: 41 to 60 Years of Age. https://www.aoa.org/healthy-eyes/eye-health-for-life/adult-vision-41-to-60-years-of-age?sso=y. Accessed March 02, 2024.
2. Holladay JT, Meyer A, Pitlick B. Phentolamine Mesylate Ophthalmic Solution Once Daily Reduces Pupil Diameter and Improves Night Vision Disturbances. AAO Annual Meeting, PA025. 2018.
3. Holland E, Karpecki P, Fingeret M, et al. Efficacy and Safety of CSF-1 (0.4% Pilocarpine Hydrochloride) in Presbyopia: Pooled Results of the NEAR Phase 3 Randomized, Clinical Trials. *Clin Ther*. 2024;46(2):104-113.
4. Martinez CE, Applegate RA, Klyce SD, McDonald MB, Medina JP, Howland HC. Effect of pupillary dilation on corneal optical aberrations after photorefractive keratectomy. *Arch Ophthalmol*. 1998;116(8):1053-1062.
5. McDonald MB, Pitlick WH, VanDevanter DR, Meyer AR, Donnenfeld ED. Phentolamine Mesylate Treatment of Severe Night Vision Complaints. AAO Annual Meetings, PO433. 2010.
6. Monestam E, Lundqvist B. Long-time results and associations between subjective visual difficulties with car driving and objective visual function 5 years after cataract surgery. *J Cataract Refract Surg*. 2006;32(1):50-55.
7. Pepose JS, Pitlick B, Meyer A, Jaber R, Charizanis K, Slonim C, et al. Phentolamine mesylate ophthalmic solution provides long lasting pupil modulation and improves visual acuity. *Invest Ophthalmol Vis Sci*. 2020;61(7):5100.
8. Pop M, Payette Y. Risk factors for night vision complaints after LASIK for myopia. *Ophthalmology*. 2004;111(1):3-10.
9. POS Investigator's Brochure; Edition 6. Ocuphire Pharma, Inc. October 28, 2022.

APPENDIX 1: IRIS COLOR CHART

Study enrollment includes both light and dark-colored eyes. Examples of light irides (pictures a, b, c, d, and e) and dark irides (pictures f, g, and h) for the purposes of this study are detailed in the chart below.



a = Light blue
b = Dark blue
c = Blue with peripupillary brown
d = Uniform green
e = Green with brown iris ring
f = Central brown and peripheral green
g = Brown with some peripheral green
h = Brown

APPENDIX 2: PARTICIPANT QUESTIONNAIRE FOR BASELINE VISIT

Participant Number: _____ Visit Date_____
Time: _____

VEGA-3 Participant Questionnaire – Baseline Visit

As you answer the participant questionnaire, please use the following examples as a reference:
***Near vision**: seeing things up close, such as a cell phone or book*
***Intermediate vision**: seeing things that are not handheld, but still close, such as the dashboard of a car or a desktop computer*
***Distance vision**: seeing things far away, such as road signs while driving or a TV screen*
***Using/doing something to manage near vision**: may include wearing reading or bifocal glasses, contact lenses, squinting, or adjusting font size or zooming in (when using screens)*

I. For **questions 1-6**, circle the answer most applicable to you, without something to manage your vision for **questions 4-6.**

1. What do you use most to help with managing your **near** vision?	Reading glasses 1	Progressive/bi-focal glasses 2	Contact Lenses 3	Squinting 4	Increase font or move objects 5

2. For how many hours in a typical day do you use or do something to help manage your **near** vision?	All waking hours 1	Working hours (e.g., 9-5) 2	Morning 3	Afternoon/ evening 4	Task-dependent 5

3. How important is clear **near** vision from the time you wake up?	Not at all important 1	Somewhat important 2	Moderately important 3	Very important 4	Extremely important 5

4. How would you describe your **near** vision in normal or day light?	Very poor 1	Poor 2	Fine 3	Good 4	Excellent 5

5. How would you describe your **near** vision in dim or evening light?	Very poor 1	Poor 2	Fine 3	Good 4	Excellent 5

6. How difficult is it for you to see **distance while driving** in dim or night light?	Very difficult 1	Moderately difficult 2	Somewhat difficult 3	A little difficult 4	Not difficult 5	I don't drive N/A

II. For each of the **questions 7-12**, circle the number that corresponds with the frequency that is most applicable to you over the past week. If you have not used screens in the past week, please circle "N/A" for **questions 9** and **10**.

Over the **past week**…	All of the time	Most of the time	Some of the time	Rarely	Never	Not applicable
7. How frequently did you use some form of **near** vision correction?	1	2	3	4	5	
8. How often did you need to use or do something to help you read small-sized text at a **near** distance (e.g., a menu or prescription label)	1	2	3	4	5	
9. How often did you need to use or do something to help you read information on a cell phone or tablet screen at a **near** distance?	1	2	3	4	5	N/A
10. How often did you need to use or do something to help you read information on a computer screen at an **intermediate** distance?	1	2	3	4	5	N/A
11. How often did you need to use or do something to help you see things clearly from a **distance**?	1	2	3	4	5	
12. How often was your self-confidence negatively affected by the ways you manage your **near** vision?	1	2	3	4	5	

Page Break

APPENDIX 3: PARTICIPANT QUESTIONNAIRE FOR VISITS 3, 4, AND 5

Participant Number: _____ Visit #_____ Date _____ Time _____

VEGA-3 Participant Questionnaire – Visits 3, 4, and 5

As you answer the participant questionnaire, please use the following examples as a reference:

***Near vision**: seeing things up close, such as a cell phone or book*

***Intermediate vision**: seeing things that are not handheld, but still close, such as the dashboard of a car or a desktop computer*

***Distance vision**: seeing things far away, such as road signs while driving or a TV screen*

***Using/doing something to manage near vision**: may include wearing reading or bifocal glasses, contact lenses, squinting, or adjusting font size or zooming in (when using screens)*

I. For each of the **questions 1-8**, circle the answer that is most applicable to your **overall experience with your study medication**.

1. My study medication made my **near** vision…	Far worse 1	Slightly worse 2	No change 3	Slightly better 4	Far better 5
2. How convenient was it to use your study medication for your **near** vision?	Very inconvenient 1	Inconvenient 2	Neutral 3	Convenient 4	Very convenient 5
3. How **frequently** would you use the study medication if it were available to you?	Never 1	Less than once a week 2	Once a week 3	2-3 times a week 4	Every day 5
4. How satisfied are you with **how long the effects** of your study medication lasted throughout the day?	Very dissatisfied 1	Dissatisfied 2	Neutral 3	Satisfied 4	Very satisfied 5
5. How satisfied are you with your study medication to help you see **clearly up close** when you first wake up?	Very dissatisfied 1	Dissatisfied 2	Neutral 3	Satisfied 4	Very satisfied 5
6. My study medication made my **near** vision in dim/low light …	Far worse 1	Slightly worse 2	No change 3	Slightly better 4	Far better 5
7. My study medication made my **distance** vision…	Far worse 1	Slightly worse 2	No change 3	Slightly better 4	Far better 5

8. My study medication made my **distance** vision while driving at night…	Far worse 1	Slightly worse 2	No change 3	Slightly better 4	Far better 5	I do not drive N/A

II. For **question 9**, please circle **every answer** that applies to you.

9. If the study medication were available to me, I would use it for…	Social settings (e.g., restaurants) 1	Work 2	Leisure (e.g., reading) 3	Phone/ tablet use 4	Driving 5	Everyday tasks (e.g., cooking) 6

III. For each of the **questions 10-13**, circle the number that corresponds with the frequency that is most applicable to you over the past week. If you have not used screens in the past week, please circle "N/A" for **questions 12** and **13**.

Over the **past week**…	All of the time	Most of the time	Some of the time	Rarely	Never	N/A
10. How frequently did you use some form of **near** vision correction?	1	2	3	4	5	
11. How often did you need to use or do something to help you read small-sized text at a **near** distance (e.g., a menu or prescription label)?	1	2	3	4	5	
12. How often did you need to use or do something to help you read information on a screen (e.g., a cell phone or tablet) at a **near** distance?	1	2	3	4	5	N/A
13. How often did you need to use or do something to help you read information on a screen at an **intermediate** distance?	1	2	3	4	5	N/A

IV. For **question 14**, circle the answer that is most applicable to you.

14. How likely would you be to use the study medication for **near** vision correction?	Extremely unlikely 1	Unlikely 2	Possibly 3	Likely 4	Extremely likely 5

APPENDIX 4: ADRENERGIC AND CHOLINERGIC DRUGS

The following drugs are examples of drugs which cannot be used within 7 days prior to Screening or during the study unless the drug, dose, and regimen has been consistent for the 7 days prior to Screening; ***however, tamsulosin is specifically excluded***. *This list is not inclusive of all drugs in these classes. If there is any doubt, please consult with the Medical Monitor.*

Alpha-1-agonists Methyl norepinephrine Naphazoline Oxymetazoline Tetrahydrozoline Phenylephrine Xylometazoline Metaraminol Methoxamine Midodrine Amidephrine *Alpha-2-agonists* Brimonidine Clonidine Guanfacine Guanabenz Guanoxabenz Guanethidine Xylazine Tizanidine Methyldopa Norepinephrine Lofexidine Medetomidine *Undetermined alpha agonists* Ergotamine Etilefrine Indanidine Mephentermine Metaraminol Methoxamine	*Non-selective alpha-antagonists* Phenoxybenzamine Tolazoline Labetalol Carvedilol Trazodone Phentolamine *Alpha-1-antagonists* Alfuzosin Prazosin Doxazosin Tamsulosin Terazosin Silodosin Fuzosin *Alpha-2-antagonists* Atipamezole Idazoxan Yohimbine Raulscine Mirtazapine	***Direct-acting acetylcholine receptor agonists*** *Choline esters* Acetylcholine Bethanechol Carbachol Methacholine *Plant alkaloids* Arecoline Nicotine Muscarine Pilocarpine ***Indirect-acting acetylcholine receptor agonists*** *Reversible cholinesterase inhibitors* Donepezil Edrophonium Neostigmine Physostigmine Pyridostigmine Rivastigmine Tacrine Caffeine Huperzine A *Irreversible cholinesterase inhibitors* Echothiophate Isoflurophate Malathion *Acetylcholine receptor antagonists* Scopolamine Dicycloverine	*Gastrointestinal* Atropine Belladonna *Parkinsonism* Amantadine Benztropine Biperiden Trihexyphenidyl ***Antimuscarinic agents*** *Antipsychotics (clozapine, quetiapine)* Atropine Benztropine Biperiden Chlorpheniramine *Certain SSRIs (Paroxetine)* Dicyclomine (Dicycloverine) Dimenhydrinate Diphenhydramine Doxepin Doxylamine Flavoxate Glycopyrrolate Glycopyrronium Hyoscyamine Ipratropium Orphenadrine Oxitropium Oxybutynin Promethazine Propantheline Bromide Scopolamine

		Tolterodine Oxybutynin Ipratropium Mamba Toxin (MT_7) Pirenzepine Telenzepine *Antivertigo* Meclizine Scopolamine	Solifenacin Tolterodine Tiotropium *Tricyclic antidepressants* Trihexyphenidyl Tropicamide Umeclidinium *Antinicotinic agents* Bupropion Dextromethorphan Doxacurium Hexamethonium Mecamylamine Tubocurarine