Clinical Study Protocol VT-001 [redacted]

A 3-Dose, Multicenter, Randomized, Double-Masked, Crossover Phase 2 Safety and Efficacy Study of BRIMOCHOL™ (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. BRIMOCHOL™ F (Carbachol /Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Monotherapy with Carbachol Topical Ophthalmic Solution in Subjects with Emmetropic Phakic and Pseudophakic Presbyopia

Sponsor:	Visus Therapeutics, Inc. 500 Yale Ave. N. Seattle, WA 98109
Medical Monitor:	[redacted]
Development Phase:	2
IND number:	150905
Clinical Trial Compliance:	This clinical trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation (ICH) and all applicable federal and local regulations.
Version and Date:	Version 9.0/ 29 July 2021

Signature Page

Sponsor Signatory:

[redacted]

07-29-21
Date

Principal Investigator Signature Page

Protocol Title	A 3-Dose, Multicenter, Randomized, Double-Masked, Crossover Phase 2 Safety and Efficacy Study of BRIMOCHOL™ (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. BRIMOCHOL™ F (Carbachol /Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Monotherapy with Carbachol Topical Ophthalmic Solution in Subjects with Emmetropic Phakic and Pseudophakic Presbyopia
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I, the undersigned, have read this protocol and agree to personally supervise conduct of this protocol in accordance with ethical principles as outlined in the ICH guidelines on GCP, any applicable laws and requirements (including Part 54: Financial Disclosure by Clinical Investigators) and any additional conditions mandated by a regulatory authority and/or Institutional Review Board (IRB).

I acknowledge that I am responsible for the overall study conduct; I approve of and will comply with all conditions, instructions, and restrictions described in this protocol. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved in writing by Visus Therapeutics, Inc. and the respective IRB.

I also agree that all information provided to me by Visus Therapeutics, Inc., including this document, Investigator's Brochure, case report form, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the Principal Investigator, or in confidence to the IRB or to the Food and Drug Administration (FDA) or other legally constituted authority.

Principal Investigator Signature	Date

Printed Name	Institution	City, State

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LIST OF ABBREVIATIONS

AE	Adverse event
AUC	Area under the curve
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration
BAK	Benzalkonium chloride
BUCDVA	Binocular uncorrected distance visual acuity
BUCNVA	Binocular uncorrected near visual acuity
COVID-19	Coronavirus Disease 2019
C_{max}	Observed maximum plasma concentration
CRA	Clinical Research Associate
CV	Coefficient of variation
D	Diopters
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GeoCV	Geometric coefficient of variation
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IOL	Intraocular lens
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MUCDVA	Monocular uncorrected distance visual acuity
MUCNVA	Monocular uncorrected near visual acuity
NRS	Numeric rating scale
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred term
OD	Oculus dexter (right eye)
OD/OS	Each eye separately
OS	Oculus sinister (left eye)
OU	Both eyes at the same time
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation

SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum plasma concentration

1 PROTOCOL SUMMARY AND SCHEDULE

1.1 Protocol Summary

Protocol Number	VT-001
Title	A 3-Dose, Multicenter, Randomized, Double-Masked, Crossover Phase 2 Safety and Efficacy Study of BRIMOCHOL™ (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. BRIMOCHOL™ F (Carbachol /Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Monotherapy with Carbachol Topical Ophthalmic Solution in Subjects with Emmetropic Phakic and Pseudophakic Presbyopia
Brief Title	Safety and Efficacy Study of BRIMOCHOL™ vs. BRIMOCHOL™ F vs. Carbachol Monotherapy Topical Ophthalmic Solutions in Subjects with Emmetropic Phakic and Pseudophakic Presbyopia
Sponsor	Visus Therapeutics, Inc.
Development Phase	2
Purpose and Rationale	Presbyopia is an inevitable, age-related, gradual loss in the ability to focus at intermediate and near targets without spectacle or surgical correction due to a progressive loss of elasticity in the crystalline lens. The pharmacologic effects of clinical studies of BRIMOCHOL suggest the addition of an alpha-2 agonist to a cholinergic agent, could have additive direct and indirect effects on both the iris constrictor and dilator muscles leading to robust and durable miosis and improvement in near visual acuity over monotherapy alone. Prior clinical studies and more recent nonclinical studies conducted by Visus demonstrate that the fixed-dose combination of BRIMOCHOL and BRIMOCHOL F both demonstrate a contribution of elements vs. the individual monotherapies formulated similarly not only on pupil size, but that iris/ciliary body carbachol area under the curve (AUC) concentrations are ~50% higher with BRIMOCHOL than carbachol alone. Ex vivo studies in bovine ciliary muscle suggest alpha-2 receptors inhibit the contraction of cholinergically innervated ciliary muscle that does not occur when the ciliary muscle is at rest. These findings support the rationale for combining an alpha-2 agonist with a cholinergic agent to minimize the adverse events (AEs) of browache/headache, myopic shift, and intraocular pressure (IOP) changes associated with cholinergics alone, and indeed, clinical studies with BRIMOCHOL suggest this is the case. There are currently no Food and Drug Administration (FDA)-approved drug products to treat presbyopia.
Study Objectives	1. To compare the efficacy, pharmacodynamics (PD), safety, tolerability and perception of treatment of topically administered, BRIMOCHOL (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination with benzalkonium chloride [BAK]) vs. BRIMOCHOL F (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination BAK-free) vs. carbachol 2.75% monotherapy BAK-free Topical Ophthalmic Solutions administered [redacted] once-daily dose in inducing miosis and improving near visual acuity among subjects with emmetropic phakic and pseudophakic presbyopia 2. To characterize the systemic pharmacokinetic (PK) profile of fixed-dose combinations BRIMOCHOL and BRIMOCHOL F topical ophthalmic solutions in subjects with emmetropic phakic and pseudophakic presbyopia

Study Design	After signing the Informed Consent Form (ICF), undergoing all Screening study assessments, and meeting all eligibility criteria at the Screening Visit, [redacted] emmetropic phakic or pseudophakic presbyopes will be randomly allocated in equal ratio to all six crossover treatment sequences to complete [redacted] subjects. Each subject will receive topically administered BRIMOCHOL 2.75% (carbachol 2.75%/brimonidine tartrate fixed-dose combination 0.1% with BAK), BRIMOCHOL F 2.75% (carbachol 2.75%/brimonidine tartrate fixed-dose combination 0.1% BAK free), and carbachol 2.75% monotherapy (BAK free) topical ophthalmic solutions [redacted] [redacted] Study drug is to be instilled in both eyes at approximately 8:00 AM ± 1 hour, by an unmasked study site personnel. at Visits [redacted] Refer to the Procedure Manual for important dosing instructions. Randomization will be stratified by whether subjects provide consent for PK sampling, and randomly assigned to one of the 3 treatment groups. [redacted] [redacted] will have blood samples for PK analysis of carbachol and brimonidine tartrate levels collected at the following times beginning at [redacted]
Study Treatment	All subjects will be randomized to receive a [redacted] dose instilled in each eye, with one of the following treatments in each phase of the study such that all subjects receive each treatment: • BRIMOCHOL (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination with BAK) Topical Ophthalmic Solution • BRIMOCHOL F (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination BAK-free) Topical Ophthalmic Solution • Carbachol 2.75% monotherapy (BAK-free) Topical Ophthalmic Solution
Study Population	[redacted] subjects with visually significant emmetropic phakic or pseudophakic presbyopia will be enrolled to complete [redacted] subjects. This will include enrolling [redacted] subjects in the PK sampling group.
Inclusion Criteria	A subject must meet the following criteria [redacted] to be eligible for inclusion in the study: 1. Male or female in good general health 2. Age 45 to 80 years, inclusive 3. Phakic in both eyes or

	Pseudophakic in both eyes following uncomplicated cataract surgery with intraocular lens (IOL) placement "in the bag" no less than 6 months prior to screening 4. Not currently wearing distance correction (spectacles or contact lenses) for daily activities 5. Visual Acuity/Refraction: a. Binocular uncorrected near visual acuity (BUCNVA) of [redacted] Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent of [redacted] or worse) under mesopic conditions, b. Binocular near visual acuity improvement [redacted] at 40 cm with pinhole occlusion compared with BUCNVA under mesopic conditions. c. Monocular uncorrected distance visual acuity (MUCDVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or better) in each eye under photopic conditions, and d. Spherical equivalent by manifest refraction not greater than ±0.50 D and cylinder not greater than 0.50 D [redacted] 6. Intraocular pressure (IOP) ≥10 mm Hg and ≤21 mm Hg 7. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate ophthalmic visual function testing and anatomic assessment 8. Normal retina and optic nerve examination 9. Not receiving eye drops in either eye other than topical artificial tears up to 2 times a day 10. Women of childbearing potential must agree to use one of the following methods of birth control from the date they sign the ICF until after the last study visit (Visit 5 or exit): a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject; b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis); c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream, AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system. Note: Non-childbearing potential is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as not having a period for at least 12 consecutive months prior to Screening). 11. Able to give informed consent and willing and able to comply with all study visits and examinations
Exclusion Criteria	A subject who meets any of the following criteria will be excluded from the study: 1. Narrow iridocorneal angles (Shaffer grade ≤2 or lower on gonioscopy examination) or previous iridotomy 2. Pupil size smaller than [redacted], under mesopic conditions, in either eye

	3. History of hyphema, microhyphema, cyclodialysis, iridodynesis, or trauma to either eye 4. Use of systemic or topical antihistamines, anticholinergics or cholinergics, or alpha-2 agonists within 90 days prior to Visit 1 or throughout the duration of the study 5. Use of systemic alpha-antagonists such as tamsulosin at any time 6. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1, or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion 7. History of participation in an interventional clinical trial investigating the use of a pharmacologic agent for treatment of cataract within 120 days and/or presbyopia within 60 days prior to Visit 1 8. Any other ocular pathology requiring treatment with topical prescription ophthalmic drops or intravitreal injection (e.g., glaucoma, allergic conjunctivitis). [redacted]. 9. Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes 10. Corneal abnormalities in either eye that interfere with visual acuity or measurement of IOP including a corneal staining grade of ≥1 central corneal staining on the National Eye Institute (NEI) corneal grading scale 11. Congenital or traumatic cataracts or congenital aphakia, central lens opacity in visual axis 12. History of intraocular surgery other than uncomplicated cataract surgery. Note: Prior LASIK refractive surgery is acceptable if the subject meets all other eligibility criteria. 13. For phakic subjects, phacodynesis or subluxation of the lens or suspected loose zonules 14. For pseudophakic subjects, complicated cataract surgery resulting in capsular tear, placement of IOL outside the bag (e.g., sulcus, scleral or iris fixation or anterior chamber placement) or yttrium aluminum garnet (YAG) capsulotomy or an axial length of ≥25 mm or multifocal or enhanced depth of focus IOLs 15. History of uveitis 16. History of pseudoexfoliation 17. Diagnosis of glaucoma or ocular hypertension or IOP of >21 mm Hg in either eye 18. Any active ocular or peri-ocular infection; any history of recurrent or chronic infection, including herpetic infection, in either eye 19. Current or previous retinal detachment or retinal pathology including age-related macular degeneration 20. Current use (within 4 weeks of Visit 1) or likely need for the use of contact lens at any time during the study 21. Concurrent disease in either eye that could require medical or surgical intervention during the study period 22. Known to be immunocompromised or receiving immunosuppression 23. History of allergic reaction to the study drug or any of its components

	24. Substance abuse (alcohol and/or drug including nicotine, marijuana, heroin, cocaine) 25. Women who are pregnant or lactating 26. Unwilling or unable to give informed consent 27. Any disease or medical condition that, in the opinion of the Investigator, would prevent the subject from participating in the study or might confound study results
Investigational and Reference Therapy	• BRIMOCHOL (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination with BAK) Topical Ophthalmic Solution • BRIMOCHOL F (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination BAK-free) Topical Ophthalmic Solution • Carbachol 2.75% monotherapy (BAK-free) Topical Ophthalmic Solution
Efficacy Assessments	Efficacy Endpoints: Primary: • Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in binocular uncorrected near visual acuity (BUCNVA) without a ≥5 ETDRS letter loss in BUCDVA at Hour 1 using both eyes under mesopic conditions • Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions • Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions • Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions • Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions [redacted]
Safety Assessments	Safety Endpoints: • Proportion of subjects with a ≥15 letter loss in photopic uncorrected distance visual acuity (MUCDVA) with monocular testing • Proportion of subjects with a ≥15 letter loss in photopic uncorrected near visual acuity (MUCNVA) with monocular testing • Ocular and non-ocular AEs

Other Assessments	Pharmacodynamic (PD) Endpoints: • Change from Baseline in pupil size in each eye at all timepoints Pharmacokinetic (PK) Endpoints: • Concentration and the following PK parameters of carbachol and brimonidine tartrate in plasma: area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration [$AUC_{(0\text{-last})}$], observed maximum plasma concentration (C_{max}), and time of maximum plasma concentration (t_{max}) [redacted]
General Statistical Methods and Types of Analyses	Analysis Populations: • *Safety Population:* All subjects who receive at least one dose of study drug will be included. Subjects will be analyzed as treated. • *Modified Intent-to-Treat (mITT) Population:* All randomized subjects who receive at least 1 dose of study drug, have the primary efficacy assessments available at Baseline (pre-dose at Hour 0 on a dosing day) and at Hour 1 (on the same dosing day) for at least 1 dosing day. • *Per Protocol (PP) Population:* All mITT subjects who do not significantly violate the protocol. The PP population will be identified prior to locking the database. • *PD Population:* All subjects who received study drug and had PD assessments will be included. • *PK Population:* All subjects who received study drug and had at least one quantifiable, post-dose plasma concentration of carbachol or brimonidine tartrate without protocol deviations or events deemed to affect the pharmacokinetics will be included. Efficacy Analyses: [redacted]

	[redacted] PD Analyses: The observed and change from baseline values of pupil size in each eye at all timepoints will be summarized with descriptive statistics by treatment, visit/day, and nominal time. At each timepoint, a Generalized Linear Mixed-effect model for repeated measures to compare between BRIMOCHOL and BRIMOCHOL F will be performed for each eye. The same will be performed to compare BRIMOCHOL F with carbachol. PK Analyses: The plasma concentrations and PK parameters of carbachol and brimonidine tartrate will be summarized with descriptive statistics by treatment and nominal sample time (concentrations only). Safety Analyses: AEs will be summarized by system organ class (SOC) and preferred term (PT), presenting the number and percentage of subjects having AEs. Severity and relationship to study drug will be listed as appropriate. Any formal statistical testing will be considered exploratory. [redacted]

	[redacted] Sample Size: The sample size of [redacted] phakic or pseudophakic presbyopia subjects is selected for determining sample size requirements and endpoint timing for Phase 3 studies and is not intended to reach statistical significance in any analysis.

1.2 Schedule of Visits and Procedures

[redacted]

[redacted]

2 BACKGROUND

2.1 Presbyopia

Presbyopia is an inevitable, age-related, gradual loss in the ability to focus at intermediate and near targets without spectacle or surgical correction due to a progressive loss of elasticity in the crystalline lens. Symptoms of presbyopia include blurred vision, ocular discomfort/headache, fatigue/drowsiness from near work, increased working distance (arms too short), and need for brighter light for reading. In childhood, an amplitude of accommodation of 12 diopters (D) is typical (Benzoni 2012). Amplitude of accommodation declines linearly at a rate of about 0.3 D per year, falling below a threshold at which near vision is noticeably impaired by approximately 40-45 years of age. An estimated 1.27 billion people have presbyopia globally, and this number is projected to increase to 1.78 billion people by 2050 (Frick 2015), including virtually all adults >50 years old.

Therapeutic approaches to presbyopia cover a spectrum of nonsurgical to surgical techniques (Moarefi 2017). Non-invasive methods of correcting presbyopia (e.g., bifocal or multifocal progressive addition lenses) can be effective, but many patients are dissatisfied for cosmetic or other reasons and desire independence from spectacles. Various surgical techniques have been applied on the cornea, lens, or sclera (Gil-Cazorla 2016). However, surgery is invasive and difficult to reverse in the event of complications or patient dissatisfaction. Moreover, surgical corrections usually require that patients choose for one eye to be corrected for distance and one for near, or monovision. Many patients do not like this outcome as this leaves them without binocular vision or depth perception at distance and near (Goertz 2014, McDonnell 2003). There are currently no Food and Drug Administration (FDA)-approved drug products to treat presbyopia.

2.2 Investigational Products

Visus Therapeutics, Inc. (Visus) is developing BRIMOCHOL (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination with BAK) and BRIMOCHOL F (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination BAK-free) Topical Ophthalmic Solutions as novel fixed-dose combination eye drops for improvement in near visual acuity in emmetropic phakic and pseudophakic presbyopia.

The active pharmaceutical ingredients carbachol and brimonidine tartrate are currently approved for topical ophthalmic use. Both carbachol and brimonidine tartrate have been used extensively in ophthalmic applications, and the approved products have been administered chronically at higher total daily doses than that in these combination products.

Five Investigator-initiated trials of a pharmacy-compounded formulation of BRIMOCHOL containing up to 3.0% carbachol and 0.2% brimonidine tartrate were conducted in presbyopic subjects; the results of 4 of these studies were published (Abdelkader 2015, 2016, 2018, 2019). These studies evaluated pupillometry and near visual acuity: across a range of carbachol concentrations from 1.5% to 3.0%, the effects of BRIMOCHOL in older and younger presbyopes and in pseudophakes, the occurrence of tachyphylaxis over 3 months, and whether the fixed-dose

combination demonstrated contribution of elements, i.e., that the combination is more effective to the individual monotherapies). These studies were not conducted by Visus.

In brief, the studies concluded that there was a dose-response to carbachol concentration with the 3% carbachol given the greatest peak and duration of effect on pupil size and near visual acuity (Abdelkader 2019). Commercially available carbachol and brimonidine tartrate was given concomitantly 5 minutes apart or as the fixed-dose BRIMOCHOL combination was more effective than carbachol and brimonidine tartrate given as monotherapy (Abdelkader 2016), suggesting contribution of elements. No tachyphylaxis was noted over 3 months of daily dosing and clinical response was comparable in subjects older or younger than 50 years of age and in pseudophakes (Abdelkader 2015). Additionally, there was no reports of headache in the largest of these studies in 57 patients (Abdelkader 2019); suggesting the addition of brimonidine tartrate may have mitigated the incidence of headache, a common adverse event associated with the use of cholinergic agents alone.

Please see the Investigator Brochure (IB) for additional information on the nonclinical and clinical support for BRIMOCHOL development.

3 RATIONALE FOR THE STUDY AND STUDY DESIGN

3.1 Therapeutic Rationale for BRIMOCHOL in Presbyopia

In recent years, various miotics have been investigated alone or in combination with one or more other agents as treatments for presbyopia (Benozzi 2012, Karanfil 2017, Renna 2017). There are two currently marketed miotic agents in the U.S.: pilocarpine (ISOPTOCARPINE [Prescribing Information]) for the lowering of intraocular pressure (IOP) and carbachol (MIOSTAT® 0.01% [Prescribing Information]) for obtaining miosis during surgery. Carbachol was also marketed as ISTOPO® CARBACHOL for the lowering of IOP for more than 50 years but was withdrawn from the market for commercial and not safety reasons. Carbachol is generally regarded as a stronger and longer-acting miotic than pilocarpine (Gelatt 1984) though with less corneal permeability with a dosing frequency of up to 2 drops 3 times daily rather than up to 4 times daily for pilocarpine.

Both carbachol and pilocarpine are parasympathomimetic agents that induce miosis by promoting contraction of the iris sphincter muscle through activation of muscarinic receptors. However, both miotics also contract the ciliary muscle, thereby reducing IOP by putting traction on the scleral spur and trabecular meshwork, thereby increasing aqueous outflow (Nardin 1966). It is also by this mechanism that miotics cause their main adverse events (AEs): browache/headache (a referred pain from the ciliary muscle contraction/spasm) and a decrease in distance acuity by inducing a myopic shift (Poinoosawmy 1976).

Brimonidine tartrate is a selective alpha-2 adrenergic agonist that works presynaptically in the management of elevated IOP to inhibit the release of norepinephrine (Kato 2018) at the nerve terminals, thereby decreasing aqueous production, episcleral venous pressure and improving trabecular outflow. By inhibiting norepinephrine's release, brimonidine tartrate's main effect at the pupil is to inhibit contraction of the iris dilator muscle, which is classically stimulated as part

of the fight-or-flight sympathetic response or, more commonly, under dark lighting to let more light into the eye.

Pupil size is modulated continuously by the opposing parasympathetic and sympathetic pathways in response to ambient lighting, accommodation, and overall sympathetic tone. The pharmacologic effects of targeting both the parasympathetic and sympathetic pathways by combining a cholinergic with an alpha-2 agonist on the pupil may be more pronounced, particularly under mesopic conditions, than observed when only one pathway is pharmacologically altered. Indeed, results of the prior clinical studies of BRIMOCHOL referenced above suggest the addition of an alpha-2 agonist leads to a more robust and durable miosis and improvement in near visual acuity over monotherapy alone. [redacted] It may be primarily by this mechanism that the prior referenced clinical study (Abdelkader 2016) demonstrated this apparent contribution of elements. Nonclinical studies conducted by Visus have demonstrated that the fixed-dose combinations BRIMOCHOL and BRIMOCHOL F not only displayed a contribution of elements in rabbits over the individual monotherapies formulated similarly on pupil size, but that iris/ciliary body carbachol area under the curve (AUC) concentrations are approximately 50% higher with the combination than carbachol alone (data on file).

Finally, prior ex vivo studies in bovine ciliary muscle suggest alpha-2 receptors inhibit the contraction of cholinergically innervated ciliary muscle that does not occur when the ciliary muscle is at rest (Kubo 1992) and may explain the absence of reported headache in prior clinical trials (Abdelkader 2019). The potential to minimize the ciliary body-induced AEs of browache/headache, myopic shift, and IOP changes associated with cholinergics alone supports the further rationale for combining an alpha-2 agonist with a cholinergic agent.

3.2 Study Rationale

The present study has been designed as a crossover study to compare the safety and efficacy of the fixed-dose combinations of BRIMOCHOL and BRIMOCHOL F and to evaluate the hypothesized contribution of elements of the BRIMOCHOL fixed-dose combinations over carbachol alone at multiple timepoints [redacted].

3.3 Rationale for Dose and Regimen Selection

Based on nonclinical studies showing an optimized BRIMOCHOL formulation performs favorably to the originally formulated 3.0% carbachol / 0.2% brimonidine tartrate, the proposed dosing regimen in this study is [redacted] administration [redacted] of BRIMOCHOL or BRIMOCHOL F topical ophthalmic solution into both eyes. [redacted]

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

- To compare the efficacy, pharmacodynamics (PD), safety, tolerability, and perception of treatment of topically administered, BRIMOCHOL (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination with BAK) vs. BRIMOCHOL F (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination BAK-free) vs. carbachol 2.75% monotherapy (BAK-free) topical ophthalmic solutions administered [redacted] once-daily dose in inducing miosis and improving near visual acuity among subjects with emmetropic phakic and pseudophakic presbyopia.
- To characterize the systemic pharmacokinetic (PK) profile of fixed-dose combinations BRIMOCHOL and BRIMOCHOL F topical ophthalmic solutions in subjects with emmetropic phakic and pseudophakic presbyopia.

4.2 Study Endpoints

4.2.1 Efficacy Endpoints

Primary

- Proportion of subjects with a ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letter gain from Baseline in binocular uncorrected near visual acuity (BUCNVA) without a ≥5 ETDRS letter loss BUCDVA at Hour 1 using both eyes under mesopic conditions
- Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions
- Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions
- Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions
- Proportion of subjects with a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA at [redacted] using both eyes under mesopic conditions

[redacted]

- [redacted]
- [redacted]

- [redacted]
- [redacted]

4.2.2 *Safety Endpoints*

- Proportion of subjects with a ≥15 letter loss in photopic uncorrected distance visual acuity with monocular testing (MUCDVA)
- Proportion of subjects with a ≥15 letter loss in photopic uncorrected near visual acuity with monocular testing (MUCNVA)
- Ocular and non-ocular AEs

4.2.3 *Pharmacodynamic (PD) Endpoints*

- Change from Baseline in pupil size in each eye at all timepoints

4.2.4 *Pharmacokinetic (PK) Endpoints*

- Concentration and the following PK parameters of carbachol and brimonidine tartrate in plasma: area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration [$AUC_{(0\text{-last})}$], observed maximum plasma concentration (C_{max}), and time of maximum plasma concentration (t_{max})

4.2.5 [redacted]

- [redacted]
- [redacted]
- [redacted]

4.2.6 [redacted]

- [redacted]
- [redacted]
- [redacted]

5 STUDY DESIGN

5.1 Study Design

This is a 3-dose, multicenter, randomized, crossover, Phase 2 safety and efficacy study in [redacted] emmetropic phakic or pseudophakic adults with presbyopia at study sites in the United States.

There will be 5 study visits with total participation for each subject of up to approximately 30 days. The study design is shown schematically in Figure 1, and the schedule of visits and procedures is provided in Section 1.2. The visits are:

- Visit 1 [redacted]
- Visit 2 [redacted]
- Visit 3: [redacted]
- Visit 4: [redacted]
- Visit 5: [redacted]

Suggested visit window is a minimum of 3 [redacted] and no more than [redacted]. [redacted] randomly allocated in equal ratio to all six crossover treatment sequences (treatment type at [redacted] will also be randomly assigned). [redacted] must occur the day following [redacted] for the [redacted]

Study drug will be instilled in both eyes at approximately 8:00 AM ± 1 hour by an unmasked study site personnel at Visits 2, 3, and 4.

Please refer to the **Procedure Manual** for important dosing instructions.

[redacted]

[redacted] of [redacted] subjects will be additionally consented such that at least [redacted] collected at the following times [redacted]

[redacted] To maintain proper masking, the interactive response technology (IRT) will monitor the process and inform the study team and investigational site to stop further PK sampling when sampling is complete.

Figure 1: Study Design Schematic

[redacted]

5.2 Beginning and End of Study

A subject is considered to be enrolled in the study when he/she has provided written, informed consent. A subject is considered to have completed the study after he/she has completed Visit 5. A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 6.4.

A subject is considered to have been lost to follow-up if he/she cannot be contacted by the Investigator. The Investigator will document efforts to attempt to reach the subject twice by telephone and will send a certified letter before considering the subject lost to follow-up. The end of participation for a subject lost to follow-up is documented as the delivery/return date of the certified letter.

Each subject will participate in the study for approximately 30 days from the time he/she signs the Informed Consent Form (ICF) through the final contact.

It is anticipated that the duration of this study will be approximately 1 month.

6 STUDY POPULATION

[redacted] adult subjects at approximately 3 sites are planned to be enrolled in this study to complete [redacted] subjects.

6.1 Inclusion Criteria

A subject must meet the following criteria at [redacted] to be eligible for inclusion in the study:

1. Male or female in good general health
2. Age 45 to 80 years, inclusive
3. Phakic in both eyes

   or

   Pseudophakic in both eyes following uncomplicated cataract surgery with intraocular lens (IOL) placement "in the bag" no less than 6 months prior to screening
4. Not currently wearing distance correction (spectacles or contact lenses) for daily activities
5. Visual Acuity/Refraction:
   a. Binocular uncorrected near visual acuity (BUCNVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or worse) under mesopic conditions,
   b. Binocular near visual acuity improvement [redacted] letters at 40 cm with pinhole occlusion compared with BUCNVA under mesopic conditions
   c. Monocular uncorrected distance visual acuity (MUCDVA) of [redacted] ETDRS Letters (Snellen equivalent of [redacted] or better) under photopic conditions, and
   d. Spherical equivalent by manifest refraction not greater than ±0.50 D and cylinder not greater than 0.50 D

   [redacted]
6. Intraocular pressure (IOP) ≥10 mm Hg and ≤21 mm Hg
7. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate ophthalmic visual function testing and anatomic assessment
8. Normal retina and optic nerve examination
9. Not receiving eye drops in either eye other than topical artificial tears up to 2 times a day

10. Women of childbearing potential must agree to use one of the following methods of birth control from the date they sign the ICF until after the last study visit (Visit 5 or exit):

    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject;

    b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis);

    c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted or injectable) or an intrauterine device or system

    Note: Non-childbearing potential is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as not having a period for at least 12 consecutive months prior to Screening).

11. Able to give informed consent and willing and able to comply with all study visits and examinations.

6.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Narrow iridocorneal angles (Shaffer grade ≤2 or lower on gonioscopy examination) or previous iridotomy

2. Pupil size smaller than [redacted], under mesopic conditions, in either eye

3. History of hyphema, microhyphema, cyclodialysis, iridodynesis, or trauma to either eye

4. Use of systemic or topical antihistamines, anticholinergics or cholinergics, or alpha-2 agonists within 90 days prior to Visit 1 or throughout the duration of the study

5. Use of systemic alpha-antagonists such as tamsulosin at any time

6. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1, or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion

7. History of participation in an interventional clinical trial investigating the use of a pharmacologic agent for treatment of cataract within 120 days and/or presbyopia within 60 days prior to Visit 1

8. Any other ocular pathology requiring treatment with topical prescription ophthalmic drops or intravitreal injection (e.g., glaucoma, allergic conjunctivitis).

[redacted]

9. Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes

10. Corneal abnormalities in either eye that interfere with visual acuity or measurement of IOP including a corneal staining grade of ≥1 central corneal staining on the National Eye Institute (NEI) corneal grading scale

11. Congenital or traumatic cataracts or congenital aphakia, central lens opacity on visual axis.

12. History of intraocular surgery other than uncomplicated cataract surgery.

    Note: Prior LASIK refractive surgery is acceptable if the subject meets all other eligibility criteria.

13. For phakic subjects, phacodynesis or subluxation of the lens or suspected loose zonules

14. For pseudophakic subjects, complicated cataract surgery resulting in capsular tear, placement of IOL outside the bag (e.g., sulcus, scleral or iris fixation or anterior chamber placement) or yttrium aluminum garnet (YAG) capsulotomy or an axial length of ≥25 mm or multifocal or enhanced depth of focus IOLs

15. History of uveitis

16. History of pseudoexfoliation

17. Diagnosis of glaucoma or ocular hypertension or IOP of >21 mm Hg in either eye

18. Any active ocular or peri-ocular infection; any history of recurrent or chronic infection, including herpetic infection, in either eye.

19. Current or previous retinal detachment or retinal pathology including age-related macular degeneration

20. Current use (within 4 weeks of Visit 1) or likely need for the use of contact lens at any time during the study

21. Concurrent disease in either eye that could require medical or surgical intervention during the study period

22. Known to be immunocompromised or receiving immunosuppression

23. History of allergic reaction to the study drug or any of its components

24. Substance abuse (alcohol and/or drug including nicotine, marijuana, heroin, cocaine)

25. Women who are pregnant or lactating

26. Unwilling or unable to give informed consent

27. Any disease or medical condition that, in the opinion of the Investigator, would prevent the subject from participating in the study or might confound study results.

6.3 Subject Re-Screening

A subject may be re-screened if the subject did not Screen Fail due to noncompliance with Screening procedures (e.g., positive urine drugs of abuse screen). The site must receive approval from the Medical Monitor prior to a subject being re-screened. If the subject is re-screened, he/she must be re-consented. Screen failure data will be recorded in the electronic case report form (eCRF), including demographics, informed consent form completion data, inclusion/exclusion criteria data, and reason for Screen Fail.

6.4 Subject Discontinuation

A subject may discontinue from the study at any time for any reason.

A subject will be withdrawn from the study if the Investigator or the Sponsor determines that it is unsafe for the subject to continue in the study. Discontinuation will be made at the discretion of the Investigator or at the subject's request.

A subject may be discontinued due to a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, or administration of non-permitted concomitant medication that might affect subject safety or study assessments/objectives. If a subject is discontinued for a reason that is related to Coronavirus Disease 2019 (COVID-19), that should be recorded.

When possible, the Sponsor should be notified before the subject is discontinued. Subjects who are discontinued from the study during a study visit should have the exit procedures completed when possible. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's eCRF.

6.5 Replacement of Subjects

A subject in the PK sampling stratum who discontinues at any time during the study may be replaced. [redacted] All replacing subjects will receive the same sequence of treatments as the replaced subjects.

7 TREATMENTS

7.1 Study Treatment

7.1.1 Randomization/Treatment Assignment

Subjects who provide informed consent will be assigned a Subject Number by the IRT. Subjects will be randomized, stratified by PK sampling group, in equal ratio [redacted]

Among the [redacted] randomized subjects, the PK sampling stratum will [redacted] subjects. Subjects who provide consent may not be required for PK sampling after [redacted] completed their blood draws. To maintain proper masking, the IRT will monitor the process and inform the study team and investigational site to stop further PK sampling.

Before the study is initiated, the login information and directions for the IRT will be provided to the registered site user(s).

7.1.2 Study Treatment

Each subject will receive [redacted] administration of each of the 3 study drugs in a masked fashion according to the assigned treatment randomization.

- BRIMOCHOL (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination with BAK) Topical Ophthalmic Solution
- BRIMOCHOL F (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination BAK-free) Topical Ophthalmic Solution
- Carbachol 2.75% monotherapy (BAK-free) Topical Ophthalmic Solution

7.1.3 Masking/Unmasking

Investigators, study site staff (except for the unmasked site personnel), and subjects will remain masked to the treatment assignment for the duration of the study. An unmasked study site personnel will be responsible for receipt of study drug shipments, dispensing, disposition, and dosing of all study drug to maintain this masking. The unmasked study personnel will avoid discussing the color of the study drug with the Investigator, other study site personnel, and the subject.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unmask study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

The IRT will be programmed with unmasking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if the unmasking of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unmasking is warranted, the Investigator should make every effort to contact the Sponsor prior to unmasking a subject's treatment assignment

unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unmasked, the Sponsor must be notified within 24 hours after breaking the masking. The date and reason that the masking was broken must be recorded in the source documentation and case report form, as applicable.

Sponsor/designee may unmask the treatment assignment for any subject with a serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

7.2 Study Drug Preparation and Dispensing

Study drug should only be handled by the unmasked study site personnel, including receipt and confirmation of new inventory. This person will be identified on the declaration of authority as the unmasked study site personnel.

At Visit 2 (Randomization), the unmasked study site personnel will confirm subject eligibility and log into the IRT to request randomization. The IRT will then randomize the subject to one of the treatment sequences and will assign a kit number to be dispensed. At subsequent treatment visits (Visit 3 and Visit 4), the unmasked study site personnel will log into the IRT to confirm the treatment visit date prior to dispensing the kit number.

For all treatment visits, the unmasked study site personnel will locate the dispensed kit number on the outer carton for the assigned kit and will open and remove the inner foil pouch. They will then confirm that the kit number on the pouch matches the kit number on the carton and will proceed to open the pouch to remove one vial for subject treatment. After the first vial has been removed and dispensed from a kit, the unmasked study site personnel will continue to dispense vials from that kit number until all vials have been used.

When instilling the study drug to subjects, the unmasked study site personnel will hold the vial so that their fingers will keep the vials' content obscured to everyone.

Study drug is instilled in each eye (a single vial contains sufficient study drug to treat both eyes). The subject will be asked to keep their eyes gently closed. Please refer to the **Procedure Manual** for important dosing instructions.

After dosing is complete, the unmasked study site personnel will immediately remove the used vial from the room. They will affix a waterproof label with the subject number onto the used vial, taking care not to cover the vial lot number, then log the dose and account for the used vial on the drug accountability sheet.

7.2.1 Study Drug Packaging and Labeling

[redacted] used to dose both eyes for a single subject.

[redacted]

7.2.2 Study Drug Storage

Study drug inventory storage conditions can be found in the **IP Manual**.

A calibrated temperature thermometer with minimum and maximum capability must be used to monitor the temperature. A temperature log must be recorded throughout the study, logging the minimum and maximum temperature once every business day.

7.2.3 Study Drug Compliance and Accountability

The Investigator is responsible for ensuring that an accurate accounting of the number of study drug (vials) inventory is received from the Sponsor, the number of units used to dose study subjects, and the number of units returned to inventory through the duration of the study.

Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time.

Only the unmasked site personnel should handle the study drug and receipt of study drug shipments. The shipment will be inspected to verify the number and condition of the study drug received and confirm receipt of the consignment in IRT.

Used vials with the affixed waterproof label will be stored in separate bags according to lot number. Each bag should be clearly marked with the lot number, and the used vials should be placed in the correct bag for the assigned lot number. Used vials will be kept for final accountability by the site monitor and return to the designated depot for reconciliation and destruction.

7.2.4 Return and Disposal of Study Drug

At the completion of the study, all used and unused study drug inventory will be returned to the designated depot for reconciliation and destruction.

7.3 Permissible Concomitant Medications/Treatments

Any medication (including ocular and over-the-counter) taken at least once within 28 days prior to the Screening Visit and during the study period will be recorded in electronic data capture (EDC), including the reason for its use.

Subjects should refrain from using any new prescription medications or changing the dose or frequency of existing therapies for the study duration (Screening to Visit 5).

7.4 Prohibited Concomitant Medications/Treatments

Medications/treatments that are prohibited prior to Visit 1 (Screening) are identified in the exclusion criteria (Section 6.2).

Use of any of the following is prohibited during the study:

- An investigational drug (other than BRIMOCHOL or BRIMOCHOL F) or device for any indication
- Systemic or topical antihistamines, anticholinergics or cholinergics, or alpha-2 agonists
- Systemic alpha-antagonists, such as tamsulosin
- [redacted]

8 STUDY VISIT SCHEDULE AND PROCEDURES

The schedule of visits and procedures is provided in Section 1.2. Details of the examinations and procedures are provided in a **Procedure Manual** and details for sample collection and processing for the clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis) and PK assessments are provided in a **Laboratory/PK Manual**.

Any delays in visits or assessments that are related to COVID-19 should be documented as such.

All subjects must sign the study ICF before beginning any Screening procedures, and a copy of the ICF must be given to the subject. The Investigator or designee must record the date when the ICF was signed in the subject's medical records.

The procedures should occur in the order presented below where possible:

8.1 Visit 1: [redacted]

1. Informed consent [redacted]
2. Demographics
3. Medical, ophthalmic, surgical history
4. Physical examination
5. Urine pregnancy test for females of childbearing potential
6. Sample collection:
    a. Hematology and clinical chemistry (whole blood)
    b. Urine (urinalysis and drug/alcohol screen)

7. AEs (Section 10.1)
8. Concomitant medications (Sections 7.3 and 7.4)
9. Electrocardiogram
10. Vital signs
11. [redacted]
12. Manifest refraction (OD/OS)
13. [redacted]
14. [redacted]
15. [redacted]
16. [redacted]
17. [redacted]
18. Slit-lamp biomicroscopy (OD/OS) with corneal staining after final evaluation
19. IOP measurement (OD/OS) after final evaluation
20. Dilated ophthalmoscopy (OD/OS) after final evaluation
21. Inclusion/exclusion criteria (Sections 6.1 and 6.2)

8.2 Visit 2[redacted] Visit 3, and Visit 4

[redacted]

1. Update medical, ophthalmic, surgical history
2. AEs (Section 10.1)
3. Concomitant medications (Sections 7.3 and 7.4)
4. Vital signs
5. Inclusion/exclusion criteria (Sections 6.1 and 6.2)

6. [redacted]
   a. [redacted]
   b. [redacted]
   c. [redacted]
   d. [redacted]
   e. Manifest refraction (OD/OS)
   f. [redacted]
   g. [redacted]
   h. [redacted]
   i. [redacted]
7. At Visit 2 only, [redacted]
8. Instillation of study drug at 8:00 AM ± 1 hour.
   Please refer to the **Procedure Manual** for important dosing instructions.
9. [redacted] (OD/OS)
10. [redacted] (OD/OS)
11. [redacted] (OD/OS)
12. [redacted]

13. [redacted]
14. [redacted]
15. [redacted]
16. [redacted]
17. [redacted]
18. Slit-lamp biomicroscopy (OD/OS) with corneal staining after final evaluation
19. IOP measurement (OD/OS) after final evaluation
20. [redacted]

8.3 Visit 5/EOS

This visit must occur the day [redacted]

1. Update medical, ophthalmic, surgical history
2. Urine pregnancy test for females of childbearing potential
3. For PK subjects only, plasma PK sample collection [redacted]
4. AEs (see Section 10.1)
5. Concomitant medications (see Section 7.3)
6. Vital signs
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. Slit-lamp biomicroscopy (OD/OS) with corneal staining after final evaluation
12. IOP measurement (OD/OS) after final evaluation
13. Dilated ophthalmoscopy (OD/OS) after final evaluation

9 PHARMACOKINETICS

At the visits and times specified in the Schedule of Visits and Procedures (Section 1.2), venous blood samples of approximately 2.5 mL each will be collected and processed to plasma to determine the plasma concentrations of carbachol and brimonidine tartrate. Instructions for the collection and handling of blood samples will be provided in a **Laboratory/PK Manual**. The actual date and time (24-hour clock time) of each sampling will be recorded.

Plasma samples will be analyzed by a laboratory approved by Visus. Concentrations of carbachol and brimonidine tartrate will be assayed using a validated method.

10 SAFETY MONITORING AND REPORTING

10.1 Adverse Events

10.1.1 Definition and Reporting

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigational subject who has been administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

AEs include:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant diseases or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study
- Loss of ≥3 lines of distance or near visual acuity

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods are also to be designated as AEs.

All AEs, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study (i.e., from Screening until EOS).

Subjects will be queried for resolution of ongoing AEs or until any unresolved AEs are judged by the Investigator to have stabilized or if lost to follow-up. Resolution of all AEs will be promptly documented by the site in the subject's CRF.

Any AE related to COVID-19 should be recorded as such.

10.2 Serious Adverse Events

10.2.1 Definitions

An SAE is any untoward medical occurrence at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., puts the subject, in the view of the Principal Investigator (PI), at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical event that may require medical or surgical intervention to prevent one of the above outcomes

An unexpected adverse drug event is any adverse drug event, the specificity or severity of which is not consistent with the current IB.

An AE is associated with the use of the drug if a reasonable possibility exists that the drug may have caused the event.

10.2.2 Reporting

SAEs that are unexpected and related to BRIMOCHOL are reportable to Regulatory Authorities. All SAEs, regardless of causality will be reported by the Investigator to the Medical Monitor through the 30-day period after the last dose of study treatment. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study treatment or study procedures must also be reported.

Report all SAEs (initial and follow-up information) on an SAE form and send the form to the Sponsor or designee within 24 hours of the discovery of the event or information (see below). The Sponsor or designee may request follow-up and other additional information from the Investigator (e.g., hospital admission or discharge notes, laboratory results). SAEs will be followed up through completion or treatment termination.

Report all deaths with the primary cause of death as the SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, report the primary cause of death on the autopsy report as the SAE term. Forward autopsy and postmortem report(s) to the Sponsor or designee, as outlined above.

If study treatment is discontinued, temporarily suspended, or the dose reduced because of an SAE, include this information in the SAE report.

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (i.e., not defined as expected in the current IB clinical study protocol, or approved labeling for marketed drugs). In this case, the Sponsor or designee will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to Investigators, according to regulatory requirements. Each Investigator must then notify his or her institutional review board (IRB) of the SUSAR as required by local regulatory authorities and in accordance with IRB policy.

10.2.3 Classification of Severity of Adverse Event

The severity of AEs will be categorized, as shown below.

Categorization of Severity of Adverse Events

Mild	The event is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); subject is aware of symptoms, but symptoms are easily tolerated.
Moderate	The event is an inconvenience or concern to the subject and causes interference with ADL, but the subject is able to continue with ADL.
Severe	The event significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL.
Potentially life-threatening	An event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

10.2.4 Relationship to Study Drug

The Investigator will make a determination of the relationship of the AE to the study drug using a 4-category system (not related, possible, probable, definite), as shown below.

Categorization for Determining Relationship of AEs to Study Treatment

Not related	An AE that does not follow a reasonable temporal sequence from administration of the drug and that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
Possible	An AE that follows a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that cannot be excluded as being possibly caused by the drug (e.g., existence of similar reports attributed to the drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
Probable	An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.
Definite	An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), follows a known or hypothesized cause-effect relationship, and (if appropriate) satisfies the following:

- Positive results obtained in drug sensitivity tests;
- Toxic level of the drug present in blood or other body fluids.

10.2.5 Ocular Events of Special Interest

For this study medically important events comprise the following ocular events, which are considered to be of special interest and by default are to be reported as SAEs:

- Decrease in visual acuity of >15 ETDRS letters or > +0.3 LogMAR in uncorrected distance visual acuity at 24 hours
- Moderate to severe intraocular inflammation (i.e., ≥2+ anterior chamber cell/flare)
- Acute angle glaucoma or moderate to severe increase in IOP of >25mm Hg
- Retinal tear or detachment

10.3 Pregnancies

Females of childbearing potential must have a negative urine pregnancy test at Visit 1 to participate. If a female has a positive urine pregnancy test during the study, the subject will be withdrawn from the study and the Investigator will notify IQVIA and/or the Sponsor within 24 hours of knowledge of the positive pregnancy test.

The pregnancy will be followed to term and/or outcome, and this outcome must be reported to the Sponsor. A pregnancy is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect, or there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method.

11 DATA COLLECTION AND MANAGEMENT

11.1 Data Confidentiality

All data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, subjects will be identified only by Subject Number and initials.

11.2 Site Monitoring

The Sponsor or designee (e.g., Clinical Research Associate [CRA]) will be responsible for monitoring this clinical trial. The CRA will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the CRA will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The Investigator will grant access to all documents (related to the study and subjects) at any time these are requested. In turn, the CRA will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and study staff will be expected to cooperate with the CRA, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

11.3 Data Collection

All primary source data or copies thereof (e.g., eCRFs, data worksheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

12 STATISTICAL METHODS AND DATA ANALYSIS

Data analysis will be performed according to the Sponsor's or designee's standard operating procedures (SOPs). A detailed statistical analysis plan (SAP) will be provided prior to database lock.

The general analytical approach for all endpoints will be descriptive in nature. Unless otherwise stated, continuous variables will be summarized using the number of subjects, mean, standard deviation (SD), median, minimum, and maximum; and categorical variables will be summarized using the frequency count and the percentage of subjects in each category.

All subject study data collected in the eCRFs will be presented in data listings.

12.1 Analysis Sets

12.1.1 Safety Population

All subjects who received any amount of study drug will be included in the Safety population. Subjects will be analyzed as treated.

12.1.2 Modified Intent-to-Treat (mITT) Population

All subjects who receive at least 1 dose of study drug, have the primary efficacy assessments available at Baseline (pre-dose at Hour 0 on a dosing day) and at Hour 1 (on the same dosing day) for at least 1 dosing day will be included in the modified Intent-to-treat (mITT) Population. Subjects will be analyzed as treated.

12.1.3 Per Protocol (PP) Population

All mITT subjects who do not significantly violate the protocol. The PP population will be identified prior to locking the database.

12.1.4 Pharmacodynamic (PD) Population

All subjects who received study drug and had at least one evaluable, post-dose PD (pupillometry) assessments without protocol deviations or events deemed to affect the PD.

12.1.5 Pharmacokinetic (PK) Population

All subjects who received study drug and had at least one quantifiable, post-dose plasma concentration of carbachol or brimonidine tartrate without protocol deviations or events deemed to affect the pharmacokinetics.

12.2 Statistical Analysis

The primary comparisons of interest in efficacy, PD, safety, and tolerance analyses are:

- BRIMOCHOL vs BRIMOCHOL F
- BRIMOCHOL F vs. carbachol alone

12.2.1 Efficacy Analyses

[redacted]

[redacted]

Specific and detailed analytic methodology will be described in the study SAP.

12.2.2 Pharmacodynamic Analyses

The PD endpoint is the change from Baseline in pupil size in each eye at all timepoints.

The individual observed and [redacted]

12.2.3 Pharmacokinetics Analyses

The following PK parameters will be derived from carbachol and brimonidine tartrate plasma concentrations using actual elapsed times from dosing, data permitting:

- $AUC_{(0\text{-last})}$: Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration
- C_{max}: Observed maximum plasma concentration
- t_{max}: Time of maximum plasma concentration

The blood sample collection times, time deviations, plasma concentrations, and PK parameters of carbachol and brimonidine tartrate will be listed based on the Safety population. The plasma concentrations and PK parameters of carbachol and brimonidine tartrate will be summarized with descriptive statistics by treatment, and concentrations additionally by nominal sample time. The descriptive statistics include the number of non-missing observations (n), mean, geometric mean, SD, CV, GeoCV, median, minimum, and maximum. For t_{max}, only n, mean, median, minimum, and maximum will be presented. These summaries will be presented using the PK population.

12.2.4 Safety Analyses

Safety assessments will be analyzed with the safety population. Safety data will be analyzed separately for [redacted] data set. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs by system organ class (SOC) and preferred term (PT). A treatment-emergent adverse event (TEAE) is a post-treatment AE where:

- there is no pre-treatment AE of the same MedDRA primary SOC and PT during the study; or
- there is a pre-treatment AE of the same MedDRA primary SOC and PT during the study, and the maximum severity during the post-treatment period is greater than that during the pre-treatment period

The number and percent of subjects reporting TEAEs will be tabulated by primary SOC and PT for each treatment. TEAEs will be further classified by severity and relationship to study drug in the summaries.

Electrocardiograms, vital signs, clinical laboratory tests, and the safety variables associated with ocular assessments (e.g., visual acuity, slit-lamp biomicroscopy, and IOP) will be summarized by treatment for each visit using appropriate descriptive statistics.

12.2.5 [redacted]

[redacted]

12.2.6 [redacted]

[redacted]

12.3 Sample Size Calculation

The study will enroll [redacted] subjects with visually significant emmetropic phakic presbyopia or pseudophakic presbyopia to complete [redacted] subjects. [redacted] The sample size is selected for determining sample size requirements and endpoint timing for Phase 3 studies and is not intended to reach statistical significance in any analysis.

13 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1 Regulatory and Ethical Compliance

The study will be conducted in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, principles enunciated in the Declaration of Helsinki, and all applicable FDA regulations.

13.2 Responsibilities of the Investigator and IRB

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. IRB approval of the protocol, informed consent document, any advertisement used to recruit study subjects must be obtained before initiating the study.

The PI is responsible for keeping the IRB advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The PI is also responsible for notifying the IRB of any reportable AEs that occur during the study.

13.3 Informed Consent Procedures

At the first visit, prior to initiation of any study-related procedures, subjects must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. The ICF must be signed and dated by the subject prior to study participation. A copy of the ICF must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by the Sponsor or its representative at any time.

Subjects included in the PK analyses will be required to sign a separate ICF.

13.4 Discontinuation of the Study

The entire study may be discontinued at the discretion of the Sponsor as specified in Section 13.10.

13.5 Publication of Study Protocol and Results

Visus will retain ownership of all data. All proposed publications based on this study will be subject to the Sponsor's approval requirements.

13.6 Study Documentation, Recordkeeping, and Retention of Documents

All study data will be captured using an EDC system. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., laboratory records, eCRFs, data worksheets, correspondence, photographs, and computer records) that are a result of the original observations

and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

The Investigator must retain study documents for a period of 2 years following the date a marketing application is approved for the study product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication until 2 years after the investigation is discontinued and the FDA is notified. The site should not destroy records until authorized to do so by Visus.

13.7 Confidentiality of Study Documents and Subject Records

All information provided regarding the study, as well as all information collected or documented during the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, subjects will be identified only by numbers and initials.

13.8 Monitoring and Quality Assurance

During the study, the Sponsor, an [redacted] CRA, or designee may complete routine monitoring visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality.

Further details of the study monitoring will be outlined in a clinical monitoring plan (CMP). Regulatory authorities of domestic and foreign agencies, the Sponsor, and [redacted] Quality Assurance and/or its designees may carry out on-site inspections and/or audits that may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits.

All inspections and audits will be carried out considering data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

13.9 Protocol Adherence

The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any changes to the protocol prior to seeking approval from the IRB. There will be no alterations in the protocol without agreement between the Sponsor and the Investigator. There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the IRB.

13.10 Study Termination

The study may be stopped at a study site at any time by the Investigator. The Sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

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15 PROTOCOL AMENDMENT [redacted]

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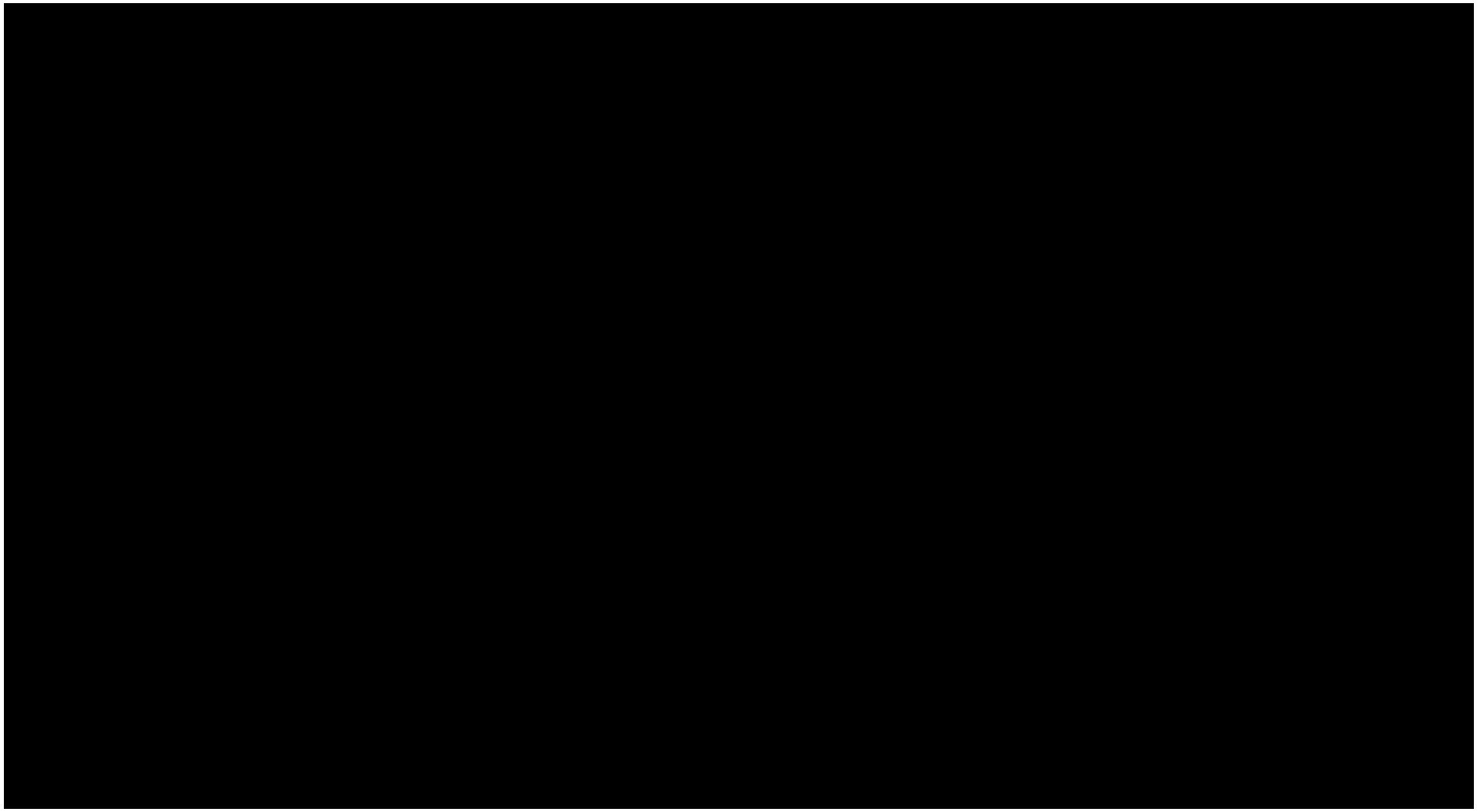

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