Clinical Trial Protocol

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-2 study: Near Eye-vision Acuity Restoration)
Protocol Number:	20-150-0003
Study Phase:	3
Investigational Product Name:	CSF-1 (pilocarpine hydrochloride 0.4% ophthalmic solution)
IND	131464
Indication:	Presbyopia
Sponsor:	Orasis Pharmaceuticals, Ltd [redacted]
Contract Research Organization:	[redacted]
IRB/IEC:	Alpha IRB 1001 Avenida Pico, Suite C, #497 San Clemente, CA 92673 949-542-3882 www.alphairb.com

	Date
Original Protocol:	August 17, 2020
Version 2.0 (Amendment 1):	January 7, 2021

Confidentiality Statement

MEDICAL MONITOR

Medical Monitor:	[redacted]

[redacted] PERSONNEL

Executive Director and Therapeutic Area Head, Posterior Segment:	[redacted]
Project Manager	[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-2 study: Near Eye-vision Acuity Restoration)
Protocol Number:	20-150-0003
Investigational Products:	• CSF-1 (pilocarpine hydrochloride 0.4% ophthalmic solution) • Vehicle
Study Phase:	3
Primary Objective:	To evaluate the efficacy of CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution) for the temporary correction of presbyopia
Secondary Objectives	To evaluate the safety and tolerability of CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution) versus Vehicle.
Overall Study Design:	
Structure:	Multi-center, randomized, double-masked, Vehicle-controlled, parallel-group, safety and efficacy study
Duration:	Approximately 3-4 weeks (screening and 3 study visits)
Controls:	Vehicle
Treatment plan:	Visit 1 (Screening, Day -14 to -1): Qualified subjects will receive 1 drop of Vehicle instilled in each eye, followed by preliminary efficacy assessments to identify Vehicle responders at 15 minutes post-vehicle instillation. Visit 2 (Day 1): Baseline assessments. Subjects who meet all inclusion and none of the exclusion criteria and qualify as Vehicle non-responders, will be randomized 1:1 to one of the following treatment arms: • CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution) • Vehicle Pre-treatment measurements taken at this visit are considered as baseline. At the Day 1 clinic visit, study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 1. Dose 2 will be instilled by study personnel at 10:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 4 hours following Dose 2. All subjects will be instructed to dose twice daily (BID) with a single drop for approximately 1 week in each eye. The first daily dose should occur in the morning, with the second dose following 2 hours later (+1 hour). Subjects will be instructed not to dose at home on clinic visit days. Visit 3 (Day 8): Study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 1. Dose 2 will be instilled by study personnel at 10:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 2. All subjects will be instructed to dose twice daily (BID) with a single drop for approximately 1 week in each eye. The first daily dose should occur in the morning with the second dose following 3 hours later (+1 hour). Subjects will be instructed not to dose at home on clinic visit days. Visit 4 (Day 15): Study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted up to 3 hours following Dose 1. Dose 2 will be instilled by study personnel at 11:30 AM ± 30

	minutes in each eye. Efficacy and safety assessments will be conducted for 5 hours following Dose 2.
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.
Study Population Characteristics:	
Number of Subjects:	Approximately 300 subjects (2 arms; 150 subjects per treatment arm) will be enrolled.
Condition/Disease:	Healthy adult subjects ages 45 to 64 years who have presbyopia
Inclusion Criteria:	Subjects must: 1. Be able and willing to provide written informed consent and sign a Health Information Portability and Accountability Act (HIPAA) form prior to any study procedure being performed; 2. Be able and willing to follow all instructions and attend study visits; 3. Be 45 to 64 years of age of either sex and any race or ethnicity at Visit 1; 4. [redacted] 8. Have a negative urine pregnancy test at Visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; 9. Be able and willing to avoid all prohibited medications for the appropriate washout periods and during the study without significant risk to the subject.
Exclusion Criteria:	Subjects must not: 1. Be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy; 2. Have known contraindications or a sensitivity to the use of any of the study drugs or their components; 3. Have an active ocular infection at Visit 1 (bacterial, viral, or fungal); 4. Have active ocular inflammation (e.g., moderate to severe blepharitis, any allergic conjunctivitis, peripheral ulcerative keratitis or scleritis) in either eye at Visit 1;

5. Have a known history or diagnosis of ocular herpetic infection, iritis, scleritis, or uveitis in either eye, whether active or inactive;
6. [redacted]
7. Be unable to or refuse to discontinue soft contact lens wear 7 days prior to study Visit 1 and rigid gas permeable (RGP) contact lens wear 14 days prior to Visit 1 and for the duration of the study;
8. Have moderate or severe dry eye defined as total corneal fluorescein staining > 2 ([redacted] Scale) in either eye at Visit 1 and/or use artificial tears or lubricant eye ointment on a daily basis;
9. Plan to use artificial tears or lubricant eye ointment on the day of or during any study visits;
10. Have clinically significant abnormal lens findings (e.g., cataract) in either eye at Visit 1;
11. [redacted]
13. Have intraocular pressure (IOP) that is < 9 millimeters of mercury (mmHg) or > 22 mmHg in either eye at Visit 1, or have a prior diagnosis of ocular hypertension or glaucoma or be currently being treated with any type of topical IOP-lowering (glaucoma) medication at Visit 1;
14. Have clinically significant abnormal findings (e.g., central corneal scar) on a slit lamp biomicroscopy exam in either eye documented at Visit 1 or a known history of a clinically significant slit-lamp finding in either eye;
15. Have clinically significant abnormal findings on a dilated indirect ophthalmoscopy exam in either eye documented at Visit 1 or a known history of a clinically significant retinal finding in either eye;
16. Have had ocular surgical intervention within 6 months prior to Visit 1, or planned surgical intervention within 30 days after Visit 4;
17. Use any of the following prohibited systemic medications during the timeframe noted below:
    a. The day of the study visit or within 12 hours prior to a study visit (chronic, daily use is <u>not</u> allowed):
        i. nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., Advil®, Motrin®)
        ii. narcotic (opiate class) pain medication (e.g., codeine, OxyContin®, Vicodin®, Tramadol®)
    b. Two (2) weeks (14 days) prior to Visit 1 or for the duration of the study:
        i. bladder medication (e.g., Urecholine®, bethanechol)
        ii. antipsychotics
        iii. antidepressants
        iv. attention-deficit/hyperactivity disorder (ADHD) medications

	v. alpha-blockers (e.g., tamsulosin [Flomax®], Jayln®, Uroxatral®, Rapaflo®) vi. anticholinergics (e.g., atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl) vii. muscarinic receptor agonists or cholinergic agonists (e.g., Salagen®, Evoxac®) other than the study drug viii. over-the-counter (OTC) or prescription antihistamines or decongestants ix. any ophthalmic medications (other than artificial tears or lubricant eye ointment [see exclusion 8 and 9 above]) x. any other medication affecting the pupil or accommodation xi. recreational drug use (e.g., marijuana, methadone, heroin, cocaine) 18. Have a diagnosis of diabetes mellitus or a history of elevated blood sugar; 19. Have a condition or a situation that in the investigator's opinion may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.
Study Treatments	• CSF-1 (pilocarpine hydrochloride 0.4% ophthalmic solution) • Vehicle
Efficacy Endpoints	**Primary Endpoints:** Percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in best distance-corrected visual acuity (BDCVA) at 40 cm (Precision Vision chart) and no loss in best distance corrected visual acuity ≥ 5 letters (ETDRS chart at 4m) in the study eye at Visit 3, following Dose 1, 1 hour post-treatment BDCVA at 40 cm is measured using an 'ETDRS-like' chart from Precision Vision. The 40 cm Precision Vision chart uses the same letter and line spacing as the ETDRS chart, only calibrated in size for testing at 40 cm. Similar to the 4m chart, the Precision Vision 40 cm chart is placed in light box creating retro illumination for testing. **Secondary Endpoints:** Percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in BDCVA at 40 cm (Precision Vision chart) and no loss in best distance corrected VA ≥ 5 letters (ETDRS chart at 4m) in the study eye at the following Visits, Doses and time points: **Visit 3 (Day 8)** **Dose 1** • Duration of Action: 2 hours following Dose 1 **Dose 2** • 1 hour following Dose 2 • Duration of Action: 2 hours following Dose 2 [redacted]

	[redacted]
Safety Endpoints	• BDCVA (normal and low luminance) at 4m • Slit-lamp biomicroscopy • Conjunctival redness grading • Study drug drop comfort assessment • IOP • Dilated indirect fundoscopy • Adverse events (AEs) (reported, elicited, and observed)

General Statistical Methods and Types of Analyses

Analysis Sets:

- Full Analysis Set – The full analysis set (FAS) will include all randomized subjects who have received at least one dose of the study drug. Subjects in the FAS will be analyzed as randomized.
- Per Protocol Set – The per-protocol (PP) set will include subjects in the FAS who do not have significant protocol deviations that affect the primary endpoint analysis. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP set will be analyzed as treated.
- Safety Set – The safety set will include all subjects who have received at least one dose of the study drug. Subjects in the safety population will be analyzed as treated.

Unit of Analysis:

The study eye will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The study eye will be defined by the study Investigator as the eye that meets all enrollment criteria. If both eyes meet all enrollment criteria, then the eye with the worse Visit 2 pre-treatment/baseline BDCVA at 40 cm (Precision Vision chart) will be the study eye. If both eyes have the same BDCVA at 40 cm, the right eye will be the study eye.

General Considerations:

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

For all variables, baseline is defined as the pre-randomization measurement taken at Visit 2 (Day 1), prior to administration of study drug. Change from baseline will be calculated as follow-up measure minus baseline measure.

Hypothesis:

The primary efficacy hypothesis is:

H_{01}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 1 = 0.

H_{11}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 1 ≠ 0.

The study will be considered a success if the null hypothesis, H_{01}, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, H_{11}, tested as delineated in the primary efficacy analysis section, and the following secondary efficacy hypotheses will each be tested as stated under adjustments for multiplicity.

The secondary efficacy hypotheses are:

Visit 3

Duration of Action Visit 3 Post-Dose 1

H_{02}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 1 = 0.

H_{12}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 1 ≠ 0.

Visit 3, 1 Hour Post-Dose 2

H_{03}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 2 = 0.

H_{13}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 2 ≠ 0.

Duration of Action Visit 3 Post-Dose 2

H_{04}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 2 = 0.

H_{14}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 2 ≠ 0.

[redacted]

[redacted]

[redacted]

[redacted]

Adjustments for Multiplicity

The following testing strategy will be employed to adjust for multiplicity:

If the primary null hypothesis, H_{01}, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, $H_{11,}$ tested as delineated in the primary efficacy analysis section, then the study will be considered a success and the following secondary hypotheses will be tested in hierarchical order, each at a 2-sided alpha = 0.05, where inference will be made on each null hypothesis only if the prior null hypotheses are rejected in favor of CSF-1

1) Visit 3 (Day 8), 2 hours following Dose 1 (H_{02})

2) Visit 3 (Day 8), 1 hour following Dose 2 (H_{03})
3) Visit 3 (Day 8), 2 hours following Dose 2 (H_{04})

[redacted]

Interim Analysis:

No interim analysis is planned for this study.

Sample Size:

A total sample size of 280 subjects (140 subjects per arm) yields >97.5% power to establish superiority of CSF-1 to Vehicle in the percentage of study eyes demonstrating a ≥ 3-line (15-letter) gain from baseline in BDCVA at

40 cm (Precision Vision chart) and no loss of best distance corrected VA ≥5 letters (ETDRS at 4m), 1-hour post each dose on Visit 3 (Day 8) assuming a response rate of 42.5% in CSF-1 and 17.5% in Vehicle using a Pearson chi-squared test with a 2-sided significance level of 0.05.

[redacted]

Accounting for approximately a 5% discontinuation rate, approximately 150 subjects per arm (approximately 300 total) will be randomized.

Estimates were obtained from the Phase 2b study (18-150-0006) Intent-to-Treat (ITT) population response for pilocarpine 0.4% vs. diclofenac (control), additionally imputing missing data as failures.

At least approximately 30% of subjects will have light (i.e., blue, green, gray, and hazel) iris, and at least approximately 30% will have a brown iris. The actual percentages will vary based on enrollment.

Primary Efficacy Analysis:

The primary efficacy endpoint in this study is the percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in best distance-corrected visual acuity (BDCVA) at 40 cm (Precision Vision chart) and no loss in best distance corrected visual acuity ≥ 5 letters (ETDRS chart) at Visit 3, 1 hour following Dose 1 in the study eye. The primary efficacy analysis will be conducted in the FAS with intercurrent events handled in the following manners:

1) Discontinuation of study drug and non-optimal compliance will be ignored [treatment policy strategy].
2) Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as failure [hypothetical strategy].
3) Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].

No subject data will be excluded from the FAS due to protocol violations/deviations. The FAS will be used for the primary efficacy analyses. Note that multiple imputations of missing values will be completed for the continuous measures (BDCVA at 40 cm and best distance corrected VA at 4m), then the response variable will be determined therefrom.

Sensitivity analyses on the primary efficacy variable will be performed using the FAS with all missing data imputed as failures, the FAS with observed data, and PP set with observed data. Additional sensitivity analyses such as control-based pattern mixture model MIs and tipping point may be performed and will be specified in the Statistical Analysis Plan (SAP).

Descriptive statistics will be presented by treatment group. Testing of the percentage of subjects with at least a 3-line (15-letter) improvement from baseline in BDCVA at 40 cm without a loss of ≥ 5 letters in best distance corrected VA at 4m will be completed separately for the 1 hour and 2 hour time points using a generalized linear mixed model with a binomial distribution including fixed effects of baseline BDCVA at 40 cm as a covariate, daily dose (Dose 1 and Dose 2), treatment, and the interaction of dose with treatment and random effect of subject to account for the correlation within a subject between daily doses. The dose-by-treatment interaction term will be used to check if there is differential treatment effect between Dose 1 and Dose 2. If the dose-by-

treatment interaction term is significant ($p < 0.10$), then the interaction term will remain in the model and testing of the treatment effect will be completed within the model separately following Dose 1 and following Dose 2. If the dose-by-treatment interaction term is not significant ($p \geq 0.10$), then the interaction term will be removed from the model and testing of treatment effect will be completed within the model pooled over dose.

The adjusted odds ratios and marginal proportions and difference in proportions along with corresponding two-sided 95% Confidence Intervals (CIs) and p-values will be presented.

Treatment comparisons will also be made separately for each time point and dose using logistic regression model including fixed effects of baseline BDCVA at 40 cm as a covariate and treatment, Pearson's chi-squared test or Fisher's exact test if any of the cell counts are less than five as a sensitivity analysis to the primary model above.

Secondary Efficacy Analysis:

For the secondary efficacy endpoints of BDCVA at 40 cm, the percentage of subjects who achieve a ≥ 3-line (15-letters) improvement from baseline without a loss of ≥ 5 letters in best distance corrected VA at 4m for each Visit, time point and daily dose (Dose 1 and Dose 2) will be summarized and analyzed using the same imputation as the primary efficacy endpoint. The same modeling strategy will be used as detailed in the primary efficacy analysis for any time point that is measured after both doses within the visit [redacted]

Exploratory Efficacy Analysis:

[redacted]

Safety Analysis:

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. Treatment Emergent AEs (TEAEs), those that occur after the first Dose of study drug, will be summarized by treatment group using frequency and percent for each System Organ Class (SOC) and Preferred Term (PT) within each SOC. Similar summaries will also be presented for serious TEAEs, TEAEs leading to death, TEAEs leading to study drug discontinuation, TEAEs related to IP and TEAEs by severity. When reporting the incidence of AEs, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT within the SOC.

Actual results and changes from baseline results in monocular and binocular BCVA at 4m and Low- Luminance BCVA, slit-lamp biomicroscopy, conjunctival redness grading, IP drop comfort, IOP, and dilated fundus examination will be summarized descriptively at each visit by treatment group.

Full details of the safety analyses will be specified in the formal SAP.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	adverse event
BCVA	best corrected visual acuity
BDCVA	best distance corrected visual acuity
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
CPMP	Committee for Proprietary Medicinal Products
eCRF	electronic case report form
CRO	clinical research organization
D	diopter
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
HIPAA	Health Information Portability and Accountability Act
LASEK	Laser-Assisted Epithelial Keratomileusis
LASIK	Laser-Assisted in-Situ Keratomileusis
LDPE	Low-Density Polyethylene
LL	Low-Luminance
LogMAR	logarithm of the minimum angle of resolution
LS	least square
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple drug imputation
mmHG	millimeters of mercury
NSAID	non-steroidal anti-inflammatory drug
OTC	over the counter
PP	per protocol
PRK	photorefractive keratectomy
PT	preferred term
RGP	rigid gas permeable
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TBD	to be determined
TEAE	treatment-emergent adverse event
VA	visual acuity

1 INTRODUCTION

Most individuals will develop symptoms of presbyopia by age 50 (Truscott 2009). Worldwide, there were 1.8 billion people globally with presbyopia in 2015, with a prevalence of approximately 25%, which is growing as the world population is aging. Approximately 45% of these cases (~826 million) had near visual impairment (VI) because of lack of or inadequate vision correction (Fricke, Tahhan et al. 2018). The primary symptom of this condition is a progressive blurring of vision when performing near tasks such as reading, sewing, working at a computer, and using a tablet or cellular phone. Other symptoms include headaches and visual fatigue, which impair one's quality of life (Truscott 2009).

The underlying cause of presbyopia is an inability to change optical power (accommodation) (Donders 1864). Accommodation is facilitated by the contraction of the ciliary muscle fibers, which change the shape and location of the crystalline lens of the eye. In response to near vision, the crystalline lens becomes thicker and more rounded in response to the actions of the ciliary muscle fibers (Garner and Yap 1997, Croft, Glasser et al. 2001, Glasser 2006). As an individual ages, the lens becomes stiffer and less amenable to changing shape in response to ciliary Muscle activity and this culminates in the symptoms of presbyopia.

Pupil size is determined by the dimensions of sphincter and dilator muscle spindles of the iris. The pupil becomes smaller in conjunction to accommodation. This reduction in the size of the pupil (termed miosis) improves the resolution of the retinal image by preventing peripheral light rays from reaching the retina. A relatively small pupil offers increased depth of field in a way similar to that achieved by reducing the aperture of a camera, leading to better visual acuity (VA) of close objects.

Current presbyopia treatment strategies include corrective lenses with single vision or bifocal/multifocal lenses, corneal refractive surgery, corneal inlay procedures, and intra-ocular lens surgery. Monovision correction improves the near vision of one eye (through the use of lenses, contacts, or surgery) while allowing the other eye to be used for distance vision. This approach has had variable results and may cause disturbances in depth-perception (Fernandez, Schwarz et al. 2013). Lastly, surgical correction of vision in presbyopia includes conductive keratoplasty, laser-assisted in-situ keratomileusis (LASIK), laser-assisted epithelial keratomileusis (LASEK), photorefractive keratectomy (PRK), corneal inlays, and accommodative or multifocal intraocular lenses (IOLs). The results of these procedures are variable, at times inconsistent, and contraindicated in some patient groups (Moussa, Jehangir et al. 2017). The inconsistencies regarding the success of some of these procedures of presbyopia treatment indicate a need for alternative strategies.

The treatment proposed here repurposes a muscarinic receptor agonist to stimulate effects on iris and ciliary contractility via stimulation of muscarinic acetylcholine receptor M3. Pilocarpine, a muscarinic agonist, has been successful in treating cases of dilated pupil following ocular surgery (Patel, Jenkins et al. 2002) and a broad spectrum of systemic conditions including botulism (Monaco, Freddi et al. 1998), leprosy (Lana-Peixoto, Campos et al. 2014), sarcoidosis (Bowie and Givre 2003), and Ross syndrome (Weller, Wilhelm et al. 1992, Chemmanam, Pandian et al. 2007).

CSF-1 was initially developed as a combination of a Non-Steroidal Anti-Inflammatory Drug (NSAID), diclofenac, with pilocarpine to reduce a potential inflammatory response associated with pilocarpine.

The safety and efficacy of CSF-1 (the initial combination and current formulation) is well established based on several previous clinical studies; an investigator-led feasibility study and two Phase 2a studies demonstrated favorable safety and preliminary efficacy.

A Phase 2b multicenter, randomized, double-masked, parallel groups, clinical study was conducted to measure the contribution of each active ingredient to the efficacy and safety of CSF-1. Subjects were assigned to one of three treatment arms; diclofenac sodium alone (0.006%), pilocarpine HCl (0.2% and 0.4%) combined with diclofenac sodium (0.006%), and pilocarpine HCl alone (0.2% and 0.4%, the latter being the current formulation). Results from this study showed that diclofenac did not significantly improve tolerability, safety or efficacy of pilocarpine in subjects with presbyopia. Furthermore, the percentage of subjects in the CSF-1 (pilocarpine HCl 0.4%/diclofenac sodium 0.006%) and pilocarpine HCl (0.4%) alone groups with ≥ 3-line improvement in monocular BCVA at 40 cm from baseline, 1-hour post-treatment at Visit 4 was statistically significant (p-value=0.0015 for CSF-1 group and p-value= 0.0002 for pilocarpine HCl group) compared to the diclofenac group, demonstrating success for the primary efficacy endpoint in the CSF-1 (pilocarpine HCl 0.4%/diclofenac sodium 0.006%) and pilocarpine HCl (0.4%) alone groups. The study thus indicated that 0.4% pilocarpine HCl as a single active ingredient was responsible for the temporary correction of presbyopia and that diclofenac is not needed in the formulation. For this reason, the Sponsor decided to continue the clinical development of CSF-1 with pilocarpine HCl 0.4% alone and to drop diclofenac from the clinical formulation

In addition, a post-hoc analysis was conducted with the additional criteria of no loss of ≥ 5 letters in distance VA to the primary endpoint. Results of this post-hoc analysis showed that 22 (43.1%) of the subjects in the CSF-1 group, and 21 (42.9%) of the subjects in the pilocarpine HCl group had a ≥3 line (15-letter) gain in BCVA at 40 cm and no loss of distance VA of ≥ 5 letters, 1-hour post-treatment at Visit 4 (Day 15) from baseline. This post-hoc analysis further solidifies the results from the Phase 2b study and suggests that not only is CSF-1 effective for the temporary correction of presbyopia (evidenced by a ≥ 3 line gain in BCVA 1-hour post-administration at Day 15 compared to baseline) but also that the benefit in BCVA at 40 cm remains after considering that no worsening of distance BCVA of ≥5 letters or more occurs. These results support the conduct of a multicenter, randomized, double masked, vehicle controlled, 2-arm, Phase 3 efficacy and safety study with the current formulation of CSF-1 (pilocarpine 0.4%) versus Vehicle, as well as define the choice of the primary end-point in the present study.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution) for the temporary correction of presbyopia.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the safety and tolerability of CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution) versus Vehicle.

3 CLINICAL HYPOTHESES

The clinical hypothesis of this study is that CSF-1 is superior and/or safer/better tolerated compared with Vehicle for improving near vision in subjects with presbyopia.

4 OVERALL STUDY DESIGN

This is a 4-visit multi-center, randomized, double-masked, parallel-group study evaluating the safety and efficacy of CSF-1 compared with Vehicle in approximately 300 subjects with presbyopia. The study design is summarized in Figure 1.

Visit 1 (Screening, Day -14 to -1): Qualified subjects will receive 1 drop of Vehicle instilled in each eye, followed by preliminary efficacy assessments to identify Vehicle responders at 15 minutes post-vehicle instillation.

Visit 2 (Day 1): Baseline assessments. Subjects who meet all inclusion and none of the exclusion criteria and qualify as Vehicle non-responders, will be randomized 1:1 to one of the following treatment arms:

- CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution)
- Vehicle

Pre-treatment measurements taken at this visit are considered as baseline.

At the Day 1 clinic visit, study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 1. Dose 2 will be instilled by study personnel at 10:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 4 hours following Dose 2.

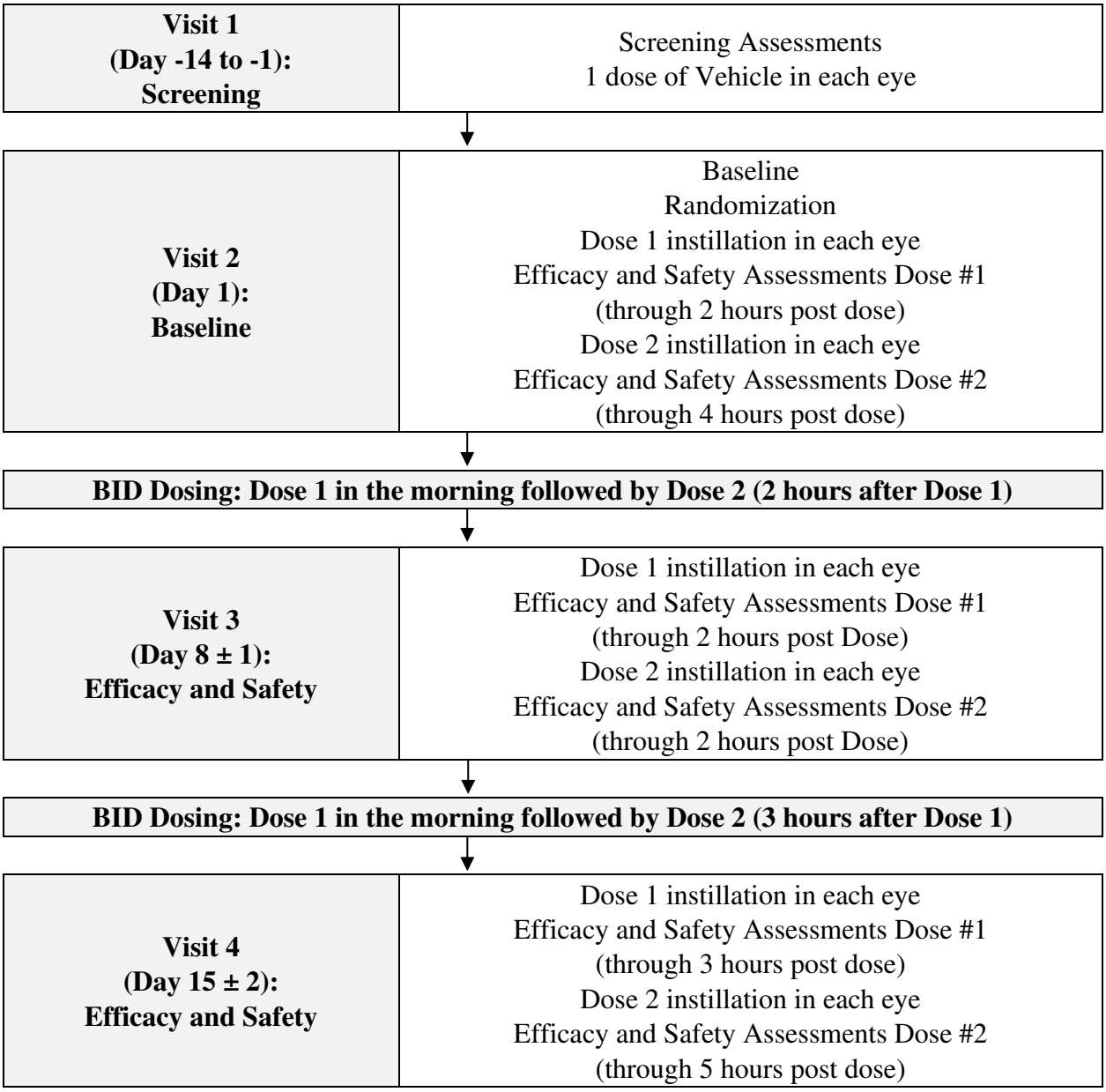
All subjects will be instructed to dose twice daily (BID) with a single drop for approximately 1 week in each eye. The first daily dose should occur in the morning, with the second dose following 2 hours later (+1 hour). Subjects will be instructed not to dose at home on clinic visit days.

Visit 3 (Day 8): Study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 1. Dose 2 will be instilled by study personnel at 10:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 2.

All subjects will be instructed to dose twice daily (BID) with a single drop for approximately 1 week in each eye. The first daily dose should occur in the morning with the second dose following 3 hours later (+1 hour). Subjects will be instructed not to dose at home on clinic visit days.

Visit 4 (Day 15): Study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted up to 3 hours following Dose 1. Dose 2 will be instilled by study personnel at 11:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 5 hours following Dose 2.

Figure 1: Study Design



5 STUDY POPULATION

Approximately, 300 healthy adult subjects (2 arms; 150 subjects per treatment arm) will be enrolled between 45 and 64 years of age with presbyopia who also meet the following criteria.

5.1 Inclusion Criteria

Subjects must:

1. Be able and willing to provide written informed consent and sign a Health Information Portability and Accountability Act (HIPAA) form prior to any study procedure being performed;
2. Be able and willing to follow all instructions and attend study visits;
3. Be 45 to 64 years of age of either sex and any race or ethnicity at Visit 1;
4. [redacted]
8. Have a negative urine pregnancy test at Visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control;
9. Be able and willing to avoid all prohibited medications for the appropriate washout periods and during the study without significant risk to the subject.

5.2 Exclusion Criteria

Subjects must not:

1. Be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy;
2. Have known contraindications or a sensitivity to the use of any of the study drugs or their components;
3. Have an active ocular infection at Visit 1 (bacterial, viral, or fungal);
4. Have active ocular inflammation (e.g., moderate to severe blepharitis, any allergic conjunctivitis, peripheral ulcerative keratitis or scleritis) in either eye at Visit 1;

5. Have a known history or diagnosis of ocular herpetic infection, iritis, scleritis, or uveitis in either eye, whether active or inactive;
6. [redacted]
7. Be unable to or refuse to discontinue soft contact lens wear 7 days prior to study Visit 1 and rigid gas permeable (RGP) contact lens wear 14 days prior to Visit 1 and for the duration of the study;
8. Have moderate or severe dry eye defined as total corneal fluorescein staining > 2 ([redacted] Scale) in either eye at Visit 1 and/or use artificial tears or lubricant eye ointment on a daily basis;
9. Plan to use artificial tears or lubricant eye ointment on the day of or during any study visits;
10. Have clinically significant abnormal lens findings (e.g., cataract) in either eye at Visit 1;
11. [redacted]
12. Have an average dark-adapted pupillometry measurement of < 3.5 mm in either eye at Visit 1;
13. Have intraocular pressure (IOP) that is < 9 millimeters of mercury (mmHg) or > 22 mmHg in either eye at Visit 1, or have a prior diagnosis of ocular hypertension or glaucoma or be currently being treated with any type of topical IOP-lowering (glaucoma) medication at Visit 1;
14. Have clinically significant abnormal findings (e.g., central corneal scar) on a slit lamp biomicroscopy exam in either eye documented at Visit 1 or a known history of a clinically significant slit-lamp finding in either eye;
15. Have clinically significant abnormal findings on a dilated indirect ophthalmoscopy exam in either eye documented at Visit 1 or a known history of a clinically significant retinal finding in either eye;
16. Have had ocular surgical intervention within 6 months prior to Visit 1, or planned surgical intervention within 30 days after Visit 4;
17. Use any of the following prohibited systemic medications during the timeframe noted below:
    a. The day of the study visit or within 12 hours prior to a study visit (chronic, daily use is <u>not</u> allowed):
        i. nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., Advil®, Motrin®)
        ii. narcotic (opiate class) pain medication (e.g., codeine, OxyContin®, Vicodin®, Tramadol®)
    b. Two (2) weeks (14 days) prior to Visit 1 or for the duration of the study:
        i. bladder medication (e.g., Urecholine®, bethanechol)

ii. antipsychotics
iii. antidepressants
iv. attention-deficit/hyperactivity disorder (ADHD) medications
v. alpha-blockers (e.g., tamsulosin [Flomax®], Jayln®, Uroxatral®, Rapaflo®)
vi. anticholinergics (e.g., atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl)
vii. muscarinic receptor agonists or cholinergic agonists (e.g., Salagen®, Evoxac®) other than the study drug
viii. over-the-counter (OTC) or prescription antihistamines or decongestants
ix. any ophthalmic medications (other than artificial tears or lubricant eye ointment [see exclusion 8 and 9 above])
x. any other medication affecting the pupil or accommodation
xi. recreational drug use (e.g., marijuana, methadone, heroin, cocaine)

18. Have a diagnosis of diabetes mellitus or a history of elevated blood sugar;
19. Have a condition or a situation that in the investigator's opinion may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.

5.3 Withdrawal Criteria

A subject may withdraw consent to participate in the study at any time for any reason. Subjects will be withdrawn from the study if any of the following criteria are met:

- Be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy; tests positive to a urine pregnancy test at Visit 4; or refuses to use an adequate method of contraception for the duration of the study;
- Have an active ocular infection (bacterial, viral, or fungal), active ocular inflammation (e.g., moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) at Visit 2, Visit 3, or Visit 4 in either eye.
- Subjects may also be withdrawn from the study for the following reasons:
    - Adverse Event (AE)
    - Lost to follow-up
    - Death
    - Subject not adequately following required study procedures
    - Study terminated by the Sponsor
    - Other

Subject withdrawals will be documented on the subjects' source document.

6 STUDY PARAMETERS

6.1 Efficacy Endpoints

Primary Efficacy Endpoints

Percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in BDCVA at 40 cm (Precision Vision chart) and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4m) in the study eye at Visit 3, following Dose 1, 1 hour post-treatment

The BDCVA at 40 cm is measured using an 'ETDRS-like' chart from Precision Vision. The 40 cm Precision Vision chart uses the same letter and line spacing as the ETDRS chart, only calibrated in size for testing at 40 cm. Similar to the 4m chart, the Precision Vision 40 cm chart is placed in light box, creating retro illumination for testing.

Secondary Efficacy Endpoints

Percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in BDCVA at 40 cm (Precision Vision chart) and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4m) in the study eye at the following Visits, Doses and time points:

Visit 3 (Day 8)

Dose 1

- Duration of Action: 2 hours following Dose 1

Dose 2

- 1 hour following Dose 2
- Duration of Action: 2 hours following Dose 2

[redacted]

Criteria for Effectiveness

Changes in BCVA at 40 cm distance will be calculated as the difference, in LogMAR units, between the post-treatment monocular (study eye) minus the baseline monocular (study eye). A 3-line improvement in VA is considered clinically meaningful.

6.2 Safety Endpoints

- BDCVA (normal and low luminance) at 4m
- Slit-lamp biomicroscopy
- Conjunctival redness grading
- Study drug drop comfort assessment
- IOP
- Dilated indirect fundoscopy
- Adverse events (AEs) (reported, elicited, and observed)

7 STUDY MATERIALS

7.1 Study Treatments

Investigational Product

The investigational product (IP) is CSF-1, a sterile topical eye drop solution. The formulation developed by Orasis Pharmaceuticals Ltd. is a preservative-free eye drop, containing the active ingredient pilocarpine hydrochloride 0.4%, with the addition of standard pharmacopoeial excipients used in sterile ophthalmic solutions.

The vehicle (CSF-1 placebo) is a topical eye drop solution containing the same ingredients as in CSF-1 except for the active ingredient.

Both IP and Vehicle are packaged in a single-dose transparent low-density polyethylene (LDPE) vials, enclosed within a pouch. Each pouch includes five vials. Kits will be dispensed to subjects at Visit 2 and Visit 3 with 1 week of at-home dosing in each kit. CSF-1 will be evaluated for comparison to Vehicle.

Instructions for Use and Administration

All study treatments are topical ophthalmic solutions that should be administered bilaterally.

Following Visit 2, all subjects will be instructed to dose twice daily (BID) with a single drop in each eye for approximately 1 week. The first daily dose should occur in the morning, with the second dose following 2 hours later (+1 hour). Subjects will be instructed not to dose at home on clinic visit days.

Following Visit 3, all subjects will be instructed to dose twice daily (BID) with a single drop in each eye for approximately 1 week. The first daily dose should occur in the morning with the second dose following 3 hours later (+1 hour). Subjects will be instructed not to dose at home on clinic visit days.

Subject Instructions

After randomization at Visit 2, subjects will receive study drug and a paper dosing diary. Once dispensed to the subject, the study drug must be stored in a refrigerator or cooler with ice pack. Study drug is packaged as a single dose unit. Subjects will remove one pouch from a single study drug kit and remove one vial from the strip. The remaining vials will be returned to the opened pouch and placed back into the refrigerator. Each subject will instill one drop of study drug to each eye and keep aside the used vial to be returned to the site at next visit for compliance check. An open vial should not be re-used. Subjects will be instructed to save and return all used and unused study drug and to bring their kits to each study visit. Following Visit 2, subjects will be instructed to dose bilaterally BID (with 2 hours (+1 hour) between doses) and record doses in their diary until Visit 3. Subjects should not dose at home on day of Visit 3. At Visit 3, subjects will receive their doses at the visit by study personnel after the required pre-treatment assessments and the current study drug will be collected. After subjects receive their study drug and dosing diary, subjects will be instructed to dose bilaterally BID (with 3 hours (+1 hour) between doses) and record doses in their diary until Visit 4. Subjects should not dose at home on day of Visit 4. At Visit 4, subjects will receive their doses at the visit by study personnel after the required pre-treatment assessments and their study drug will be collected. Subjects will exit the study after all assessments are complete at Visit 4.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

Overview

Subjects as defined by the criteria in Section 5.1 and Section 5.2 will be considered for entry into this study.

Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study-related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an Informed Consent Form (ICF) and other written documentation in accordance with local privacy requirements (where applicable). Additional information can be found in Section 11.1.1.

Washout Intervals

- Use any of the following prohibited systemic medications during the timeframe noted below:
    - The day of the study visit or within 12 hours prior to a study visit (chronic, daily use is not allowed):
        - nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., Advil®, Motrin®)
        - narcotic (opiate class) pain medication (e.g., codeine, OxyContin®, Vicodin®, Tramadol®)
    - Two (2) weeks (14 days) prior to Visit 1 or for the duration of the study:
        - bladder medication (e.g., Urecholine®, bethanechol)
        - antipsychotics
        - antidepressants
        - attention-deficit/hyperactivity disorder (ADHD) medications
        - alpha-blockers (e.g., tamsulosin [Flomax®], Jayln®, Uroxatral®, Rapaflo®)
        - anticholinergics (e.g., atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl)
        - muscarinic receptor agonists or cholinergic agonists (e.g., Salagen®, Evoxac®) other than the study drug
        - over-the-counter (OTC) or prescription antihistamines or decongestants
        - any ophthalmic medications (other than artificial tears or lubricant eye ointment [see exclusion 8 and 9 above])
        - any other medication affecting the pupil or accommodation
        - recreational drug use (e.g., marijuana, methadone, heroin, cocaine)

Procedures for Final Study Entry

Subjects must satisfy all inclusion and none of the exclusion criteria in order to be entered into the study.

Pregnancy

Females must have a negative urine pregnancy test at Visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last

menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

In the event a female has a positive urine pregnancy test at Visit 4, the subject will be withdrawn from the study and the investigator will notify [redacted] and the sponsor within 24 hours of knowledge of the positive pregnancy test.

Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a subject number. Subject numbers will be assigned in sequential order beginning with 001. Once a subject meets all qualification criteria at Visit 2, he/she will be randomized in a 1:1 ratio via an Interactive Response Technology (IRT) system to one of the following treatment groups: 1: CSF-1 (pilocarpine hydrochloride 0.4% ophthalmic solution), 2: Vehicle, and stratified by iris color (brown versus light [i.e., blue, green, gray, and hazel]) and by baseline manifest refraction spherical equivalent (-4.5 D to <-0.5 D, -0.5 D to +0.75 D, and >+0.75 D to +2.0 D); randomization will not be stratified by site.

At least approximately 30% of subjects will have light (i.e., blue, green, gray, and hazel) iris and at least approximately 30% will have a brown iris. The actual percentages will vary based on enrollment.

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., iris color and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.

8.2 Concurrent Therapies and Medical History

The use of any concurrent medication, prescription, or OTC taken within 30 days of Visit 1, is to be recorded on the subjects' source document and corresponding electronic Case Report Form (eCRF) along with the reason the medication was taken.

All significant current and prior ocular medical and surgical history are to be recorded on the subjects' source document and corresponding eCRF. All current and prior significant general medical and surgical history is to be recorded on the subject's source document and corresponding eCRF.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

Prohibited Medications/Treatments

Washout intervals as described in Section 8.1.2 should be followed for all prohibited medications. Soft contact lenses must be removed at least 7 days prior to study Visit 1 and during the study, and RGP contact lenses must be removed at least 14 days prior to study Visit 1 and during the study.

8.3 Examination Procedures

8.3.1 Procedures to be performed at the Study Visit with Regard to Study Objective

[redacted]

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

[redacted]

The following procedures should be conducted at each study visit in the following order:

8.3.1.1 Visit 1 (Day -14 to -1)

1. Informed consent/HIPAA
2. Demographic data
3. Medical and medication history
4. Urine pregnancy test (for females of child-bearing potential)
5. Inclusion and exclusion criteria review

[redacted]

[redacted]

8.3.1.2 Visit 2 (Day 1)

1. Medical and medication history update
2. Inclusion and exclusion criteria review

[redacted]

[redacted]

30. Dispense study drug/dosing diary

8.3.1.3 Visit 3 (Day 8 ± 1)

1. Medical and medication history update

[redacted]

[redacted]

27. Dispense study drug/dosing diary
28. Collect study drug/dosing diary

8.3.1.4 Visit 4 (Day 15 ± 2)

1. Medical and medication history update

[redacted]

[redacted]

30. Study exit

8.4 Schedule of Visits, Measurements, and Dosing

Scheduled Visit

Refer to Appendix 1: Schedule of Visits and Measurements for a schedule of measurements at the visit.

Unscheduled Visits

In the case of an AE, an unscheduled visit may occur. The investigator may perform additional assessments at their discretion. All additional assessments will be documented in the subject's source document.

8.5 Compliance with Protocol

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) Committee for Proprietary Medicinal Products (CPMP/ICH/135/95), and applicable regulatory requirement(s), such as Food and Drug Administration (FDA) GCP Regulations and Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312, as appropriate.

8.6 Subject Disposition

Completed Subjects

A completed subject is one who has not been discontinued from the study and successfully completes all 4 study visits.

Withdrawn Subjects

A subject may be withdrawn for meeting any of the withdrawal criteria as described in Section 5.3.

Discontinued Subjects

A discontinued subject is one who does not complete the protocol-defined study visits. A subject may be discontinued at the discretion of the investigator, sponsor, and/or the Institutional Review

Board (IRB). Notification of early discontinuation from the study and the reason for discontinuation will be made to the sponsor and/or [redacted]

Prior to discontinuing a subject, every effort should be made to obtain as much follow-up data as possible, and to retrieve all study materials. AEs will be followed as described in Section 9.

8.7 Study Termination

The study may be terminated at any time by the investigator, the sponsor, and/or [redacted] with appropriate notification.

8.8 Study Duration

This study is comprised of a screening period and 4 study visits over a duration of approximately 3 to 4 weeks.

8.9 Monitoring and Quality Assurance

During the course of the study the Sponsor, an [redacted] monitor, or designee, may make routine site visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to the pertinent 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 monitoring plan.

Regulatory authorities of domestic and foreign agencies, the Sponsor, and [redacted] Inc. 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 giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of an IP in humans, whether it is considered IP-related or not. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the subject's source document and eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to IP, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

All AEs will be collected from the time a subject signs the ICF through the subjects' study exit visit.

Severity

The severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the IP caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the IP caused the AE.

"Suspected adverse reaction" means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly

associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- *Unexpected*: an AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.
- *Not applicable:* an AE unrelated to IP.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological (or other) properties of the product but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE. The final classification of an AE is subject to the sponsor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if < 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/Phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

Note: A Serious Adverse Event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., intraocular hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. The medical monitor will review and determine the expectedness of any SAE following the investigator's assessment.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to [redacted], the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate subject source document and eCRF.

Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to [redacted] the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the study drug, must be immediately reported by the investigator to [redacted] and the sponsor within 24 hours of becoming aware of the event. All information relevant to the SAE must be recorded on the appropriate source document, SAE Report Form, and eCRF, including all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject, a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP. The investigator must also inform the IRB of the AE within their guidelines for reporting SAEs. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the sponsor in addition to the information reported on the source document, SAE Report Form, and eCRF. All subjects experiencing an SAE must be followed-up with, and the outcome reported.

Contact information for reporting SAEs:

[redacted]

9.4 Procedures for Unmasking (if applicable)

Treatment assignment should not be communicated to the Contract Research Organization (CRO) or Sponsor and should not be recorded in any study documents or source document. When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. When possible (i.e., in non-emergency situations), [redacted] and/or the study sponsor should be notified before unmasking the study drug.

Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution, until the subject is lost to follow-up or until the AE is otherwise explained. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subjects' source document. Non-serious AEs identified on the last scheduled contact must be recorded on the source document with the status noted.

If the investigator becomes aware of any new information regarding an SAE (i.e., resolution, change in condition, or new treatment), a new SAE Report Form must be completed and faxed/emailed to [redacted] and/or the study sponsor within 24 hours. The original SAE Report Form is not to be altered. The SAE Report Form should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 General Considerations

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

For all variables, baseline is defined as the pre-randomization measurement taken at Visit 2 (Day 1), prior to administration of study drug. Change from baseline will be calculated as follow-up measure minus baseline measure.

10.2 Hypotheses

The primary efficacy hypothesis is:

H_{01}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 1 = 0.

H_{11}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 1 ≠ 0.

The study will be considered a success if the null hypothesis, H01, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, H11, tested as delineated in the primary efficacy analysis section, and the following secondary efficacy hypotheses will each be tested as stated under adjustments for multiplicity.

The secondary efficacy hypotheses are:

Visit 3

Duration of Action Visit 3 Post-Dose 1

H_{02}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 1 = 0.

H_{12}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 1 ≠ 0.

Visit 3, 1 Hour Post-Dose 2

H_{03}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 2 = 0.

H_{13}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 1 hour post-Dose 2 ≠ 0.

Duration of Action Visit 3 Post-Dose 2

H_{04}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 2 = 0.

H_{14}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in best distance corrected VA of ≥ 5 letters (ETDRS at 4m) at Visit 3 (Day 8), 2 hours post-Dose 2 ≠ 0.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Adjustments for Multiplicity

The following testing strategy will be employed to adjust for multiplicity:

If the primary null hypothesis, H_{01}, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, $H_{11,}$ tested as delineated in the primary efficacy analysis section, then the study will be considered a success and the following secondary hypotheses will be tested in hierarchical order, each at a 2-sided alpha = 0.05, where inference will be made on each null hypothesis only if the prior null hypotheses are rejected in favor of CSF-1

1) Visit 3 (Day 8), 2 hours following Dose 1 (H_{02})
2) Visit 3 (Day 8), 1 hour following Dose 2 (H_{03})
3) Visit 3 (Day 8), 2 hours following Dose 2 (H_{04})

[redacted]

[redacted]

10.3 Study Populations

- Full Analysis Set – The full analysis set (FAS) will include all randomized subjects who have received at least one dose of the study drug. Subjects in the FAS will be analyzed as randomized.
- Per Protocol Set – The per-protocol (PP) set will include subjects in the FAS who do not have significant protocol deviations that affect the primary endpoint analysis. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP set will be analyzed as treated.
- Safety Set – The safety set will include all subjects who have received at least one dose of the study drug. Subjects in the safety population will be analyzed as treated.

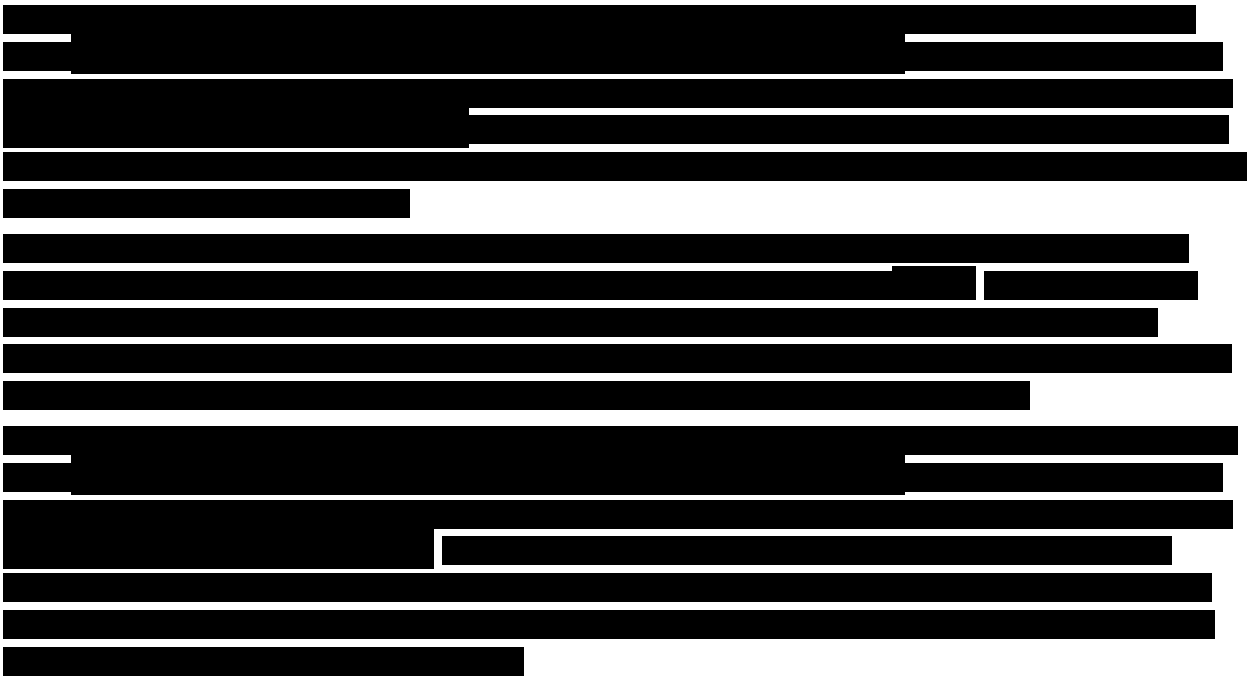
10.4 Unit of Analysis

The study eye will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The study eye will be defined by the study Investigator as the eye that meets all enrollment criteria. If both eyes meet all enrollment criteria, then the eye with the worse Visit 2 pre-treatment/baseline BDCVA at 40 cm (Precision Vision chart) will be the study eye. If both eyes have the same BDCVA at 40 cm, the right eye will be the study eye.

10.5 Sample Size

A total sample size of 280 subjects (140 subjects per arm) yields >97.5% power to establish superiority of CSF-1 to Vehicle in the percentage of study eyes demonstrating a ≥ 3-line (15-letter) gain from baseline in BDCVA at 40 cm (Precision Vision chart) and no loss of best distance corrected VA ≥5 letters (ETDRS at 4m), 1-hour post each dose on Visit 3 (Day 8) assuming a response rate of 42.5% in CSF-1 and 17.5% in Vehicle using a Pearson chi-squared test with a 2-sided significance level of 0.05.



Accounting for approximately a 5% discontinuation rate, approximately 150 subjects per arm (approximately 300 total) will be randomized.

Estimates were obtained from the Phase 2 study (18-150-0006) Intent-to-Treat (ITT) population response for pilocarpine 0.4% vs. diclofenac (control), additionally imputing missing data as failures.

At least approximately 30% of subjects will have light (i.e., blue, green, gray, and hazel) iris, and at least approximately 30% will have a brown iris. The actual percentages will vary based on enrollment.

10.6 Demographic and Baseline Characteristics

Subject demographics including age, gender, race, ethnicity, and iris color will be presented using summary statistics (mean, SD, minimum, maximum, and median) or frequency counts and percentages as appropriate.

10.7 Efficacy Analysis

Primary Efficacy Analyses

The primary efficacy endpoint in this study is the percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in best distance-corrected visual acuity (BDCVA) at 40 cm (Precision Vision chart) and no loss in best distance corrected visual acuity ≥ 5 letters (ETDRS chart) at Visit 3, 1 hour following Dose 1 in the study eye. The primary efficacy analysis will be conducted in the FAS with intercurrent events handled in the following manners:

1) Discontinuation of study drug and non-optimal compliance will be ignored [treatment policy strategy].
2) Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as failure [hypothetical strategy].
3) Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].

No subject data will be excluded from the FAS due to protocol violations/deviations. The FAS will be used for the primary efficacy analyses. Note that multiple imputations of missing values will be completed for the continuous measures (BDCVA at 40 cm and best distance corrected VA at 4m), then the response variable will be determined therefrom.

[redacted]

Descriptive statistics will be presented by treatment group. Testing of the percentage of subjects with at least a 3-line (15-letter) improvement from baseline in BDCVA at 40 cm without a loss of ≥ 5 letters in best distance corrected VA at 4m will be completed separately for the 1 hour and 2 hour time points using a generalized linear mixed model with a binomial distribution including fixed effects of baseline BDCVA at 40 cm as a covariate, daily dose (Dose 1 and Dose 2), treatment, and the interaction of dose with treatment and random effect of subject to account for the correlation within a subject between daily doses. [redacted]

The adjusted odds ratios and marginal proportions and difference in proportions along with corresponding two-sided 95% Confidence Intervals (CIs) and p-values will be presented.

Treatment comparisons will also be made separately for each time point and dose using logistic regression model including fixed effects of baseline BDCVA at 40 cm as a covariate and treatment, Pearson's chi-squared test or Fisher's exact test if any of the cell counts are less than five as a sensitivity analysis to the primary model above.

Secondary Efficacy Analysis

For the secondary efficacy endpoints of BDCVA at 40 cm, the percentage of subjects who achieve a ≥ 3-line (15-letters) improvement from baseline without a loss of ≥ 5 letters in best distance corrected VA at 4m for each Visit, time point and daily dose (Dose 1 and Dose 2) will be summarized and analyzed using the same imputation as the primary efficacy endpoint. The same modeling strategy will be used as detailed in the primary efficacy analysis for any time point that is measured after both doses within the visit [e.g.: 2 hours at Visit 3 (Day 8); 30 minutes, 1 and 2 hours at Visit 2 (Day 1); and 20 minutes, 1, 2, and 3 hours at Visit 4 (Day 15)]. For those time points that are measured only after the second dose within the visit [redacted]

[redacted]

10.8 Safety Analysis

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. Treatment Emergent AEs (TEAEs), those that occur after the first dose of study drug, will be summarized by treatment group using frequency and percent for each System Organ Class (SOC) and Preferred Term (PT) within each SOC. Similar summaries will also be presented for serious TEAEs, TEAEs leading to death, TEAEs leading to study drug discontinuation, TEAEs related to IP and TEAEs by severity. When reporting the incidence of AEs, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT within the SOC.

Actual results and changes from baseline results in monocular and binocular BCVA at 4m and Low- Luminance BCVA, slit-lamp biomicroscopy, conjunctival redness grading, IP drop comfort, IOP, and dilated fundus examination will be summarized descriptively at each visit by treatment group.

Full details of the safety analyses will be specified in the formal SAP.

10.9 Interim Analysis

No interim analyses are planned for this study.

10.10 Missing Data

The primary efficacy analyses will be conducted with missing data and intercurrent events handled in the following manners:

1) Discontinuation of study drug and non-optimal compliance will be ignored [treatment policy strategy].
2) Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as failure [hypothetical strategy].
3) Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].

Sensitivity analyses on the primary efficacy variable will be performed using the FAS with all missing data imputed as failures, the FAS with observed data, and PP set with observed data. Additional sensitivity analyses such as control-based pattern mixture model MIs and tipping point may be performed and will be specified in the Statistical Analysis Plan (SAP).

10.11 Adjustment for Multiplicity

If the primary null hypothesis, H_{01}, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, $H_{11,}$ tested as delineated in the primary efficacy analysis section, then the study will be considered a success and the following secondary hypotheses will be tested in hierarchical order, each at a 2-sided alpha = 0.05, where inference will be made on each null hypothesis only if the prior null hypotheses are rejected in favor of CSF-1

1. Visit 3 (Day 8), 2 hours following Dose 1 (H_{02})
2. Visit 3 (Day 8), 1 hour following Dose 2 (H_{03})
3. Visit 3 (Day 8), 2 hours following Dose 2 (H_{04})

[redacted]

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current GCPs, including the ICH Guidelines, and will, in general, be consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drug in the countries involved will be adhered to.

11.1 Protection of Human Subjects

Subject Informed Consent

Informed consent must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subjects' parent or legal guardian prior to enrollment into the study.

All ICFs must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the ICF requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by [redacted] prior to submission to the governing IRB and that it is read, signed, and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

All subjects have the right to withdraw consent at any time during the study period. If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by [redacted] and/or the sponsor and provided in writing by [redacted] and/or the sponsor prior to the consent process.

IRB Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB-approved version of the ICF will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [redacted] the sponsor, the IRB approving this study, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subjects' original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed in, but the subjects' identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigators' subject files, as well as the results of diagnostic tests such as radiographs, laboratory tests, and electrocardiograms. The investigators' copy of the eCRFs serves as the investigators' record of a subjects' study-related data.

Retention of Documentation

All study-related correspondence, patient records, consent forms, records of the distribution and use of all study drug, and copies of case report forms should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept

the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

Labeling/Packaging

Vehicle for screening and study drug will be packaged and labeled into clinical kits for screening and treatment. Vehicle for screening will be labeled and packaged into screening kits containing 1 pouch each. After randomization, each subject will be assigned a single master kit containing two smaller (inner) kits of study drug for treatment. Each inner kit will be comprised of 5 pouches containing one strip of 5 vials containing IP or vehicle. Each master kit will be uniquely identified by the kit number; the 2 inner kits inside will bear the same kit number with an additional designation indicating the visit at which each is to be dispensed (i.e., Visit 2 or Visit 3). Screening kit, master kit, and inner kit labels will also include a space for the site to enter each subjects' subject number and initials upon kit assignment.

Clinical label texts for the packaging will meet applicable regulatory requirements and include the statement "Caution: New Drug-Limited by Federal Law to Investigational Use."

Storage of Investigational Product

Study drug and Vehicle for screening must be stored in a secure area of the investigative site, accessible only to the investigator or designees, refrigerated between 2° to 8°C (36° to 46°F). A temperature log must be recorded throughout the course of the study, once every business day with the minimum and maximum temperature. Study drug will be administered/dispensed only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. Subjects will be instructed to store dispensed study drug under refrigerated conditions, and transport study drug kits to their homes using cooler bags and an ice pack provided by the site at the time of dispensation. All study drug will be returned to inventory after use in the provided return bags. Please refer to the IP manual for additional information.

Accountability of Study Drug

Study drug (IP and Vehicle) is to only be administered by study personnel and is to only be used in accordance with this protocol. Study drug must only be distributed to subjects properly qualified under this protocol to receive study drug.

Sites must keep an accurate accounting of the study drug received from the supplier. This includes the amount of study drug administered to subjects and the amount returned or disposed throughout the course of the study. A detailed inventory must be completed for the study drug.

Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee or destroyed. The return or disposal of study drug will be specified in writing. Any remaining study drug will be collected from the subject at Visit 3 and Visit 4 before study exit. Further details on labeling, packaging, storage, accountability, and return or disposal of study drug can be found in the IP Manual.

11.6 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subjects' source document, eCRF, and all study-related material. All study data should

also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when by adding to the correction his/her initials as well as the date of the correction.

11.7 Handling of Biological Specimens

Not applicable

12 PUBLICATIONS

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. [redacted] and the study sponsor will have the final decision regarding the manuscript and publication.

13 REFERENCES

Bowie, E. M. and S. J. Givre (2003). "Tonic pupil and sarcoidosis." Am J Ophthalmol **135**(3): 417-419.

Chemmanam, T., J. D. Pandian, R. S. Kadyan and S. M. Bhatti (2007). "Anhidrosis: a clue to an underlying autonomic disorder." J Clin Neurosci **14**(1): 94-96.

Croft, M. A., A. Glasser and P. L. Kaufman (2001). "Accommodation and presbyopia." Int Ophthalmol Clin **41**(2): 33-46.

Donders, F. C. (1864). Accommodation and refraction of the eye Translated by WD Moore 1952 The New Sydenham Society/Hatton Press, London.

Fernandez, E. J., C. Schwarz, P. M. Prieto, S. Manzanera and P. Artal (2013). "Impact on stereo-acuity of two presbyopia correction approaches: monovision and small aperture inlay." Biomed Opt Express **4**(6): 822-830.

Fricke, T. R., N. Tahhan, S. Resnikoff, E. Papas, A. Burnett, S. M. Ho, T. Naduvilath and K. S. Naidoo (2018). "Global Prevalence of Presbyopia and Vision Impairment from Uncorrected Presbyopia: Systematic Review, Meta-analysis, and Modelling." Ophthalmology **125**(10): 1492-1499.

Garner, L. F. and M. K. Yap (1997). "Changes in ocular dimensions and refraction with accommodation." Ophthalmic Physiol Opt **17**(1): 12-17.

Glasser, A. (2006). "Accommodation: mechanism and measurement." Ophthalmol Clin North Am **19**(1): 1-12, v.

Lana-Peixoto, M. A., W. R. Campos, P. A. Reis, C. M. Campos and C. A. Rodrigues (2014). "Tonic pupil in leprosy." Arq Bras Oftalmol **77**(6): 395-396.

Monaco, S., N. Freddi, E. Francavilla, F. Meneghetti, L. Fenicia, G. Franciosa and P. Cadrobbi (1998). "Transient tonic pupils in botulism type B." J Neurol Sci **156**(1): 96-98.

Moussa, K., N. Jehangir, T. Mannis, W. L. Wong and M. Moshirfar (2017). "Corneal Refractive Procedures for the Treatment of Presbyopia." Open Ophthalmol J **11**: 59-75.

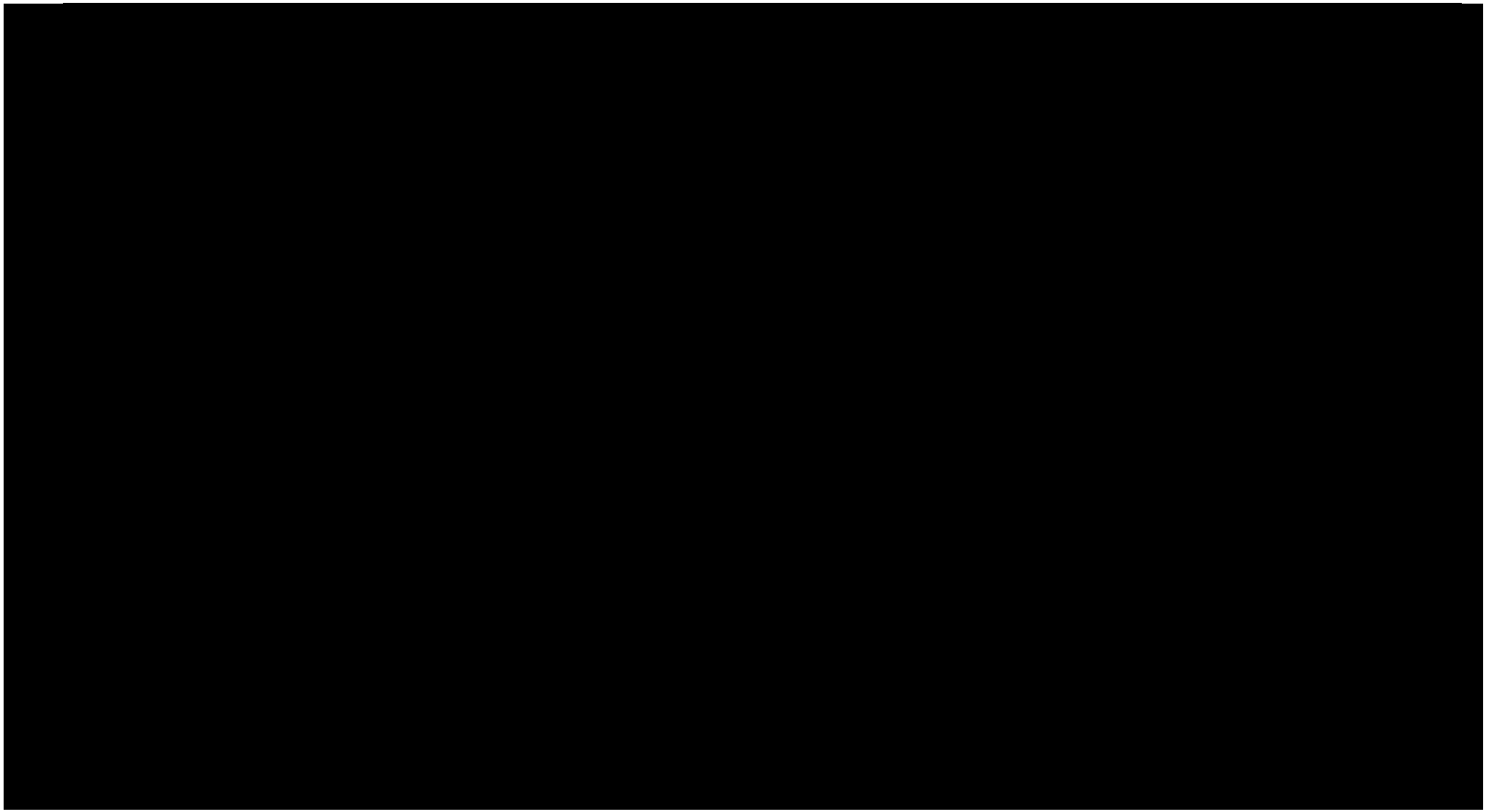
Patel, J. I., L. Jenkins, L. Benjamin and S. Webber (2002). "Dilated pupils and loss of accommodation following diode panretinal photocoagulation with sub-tenon local anaesthetic in four cases." Eye (Lond) **16**(5): 628-632.

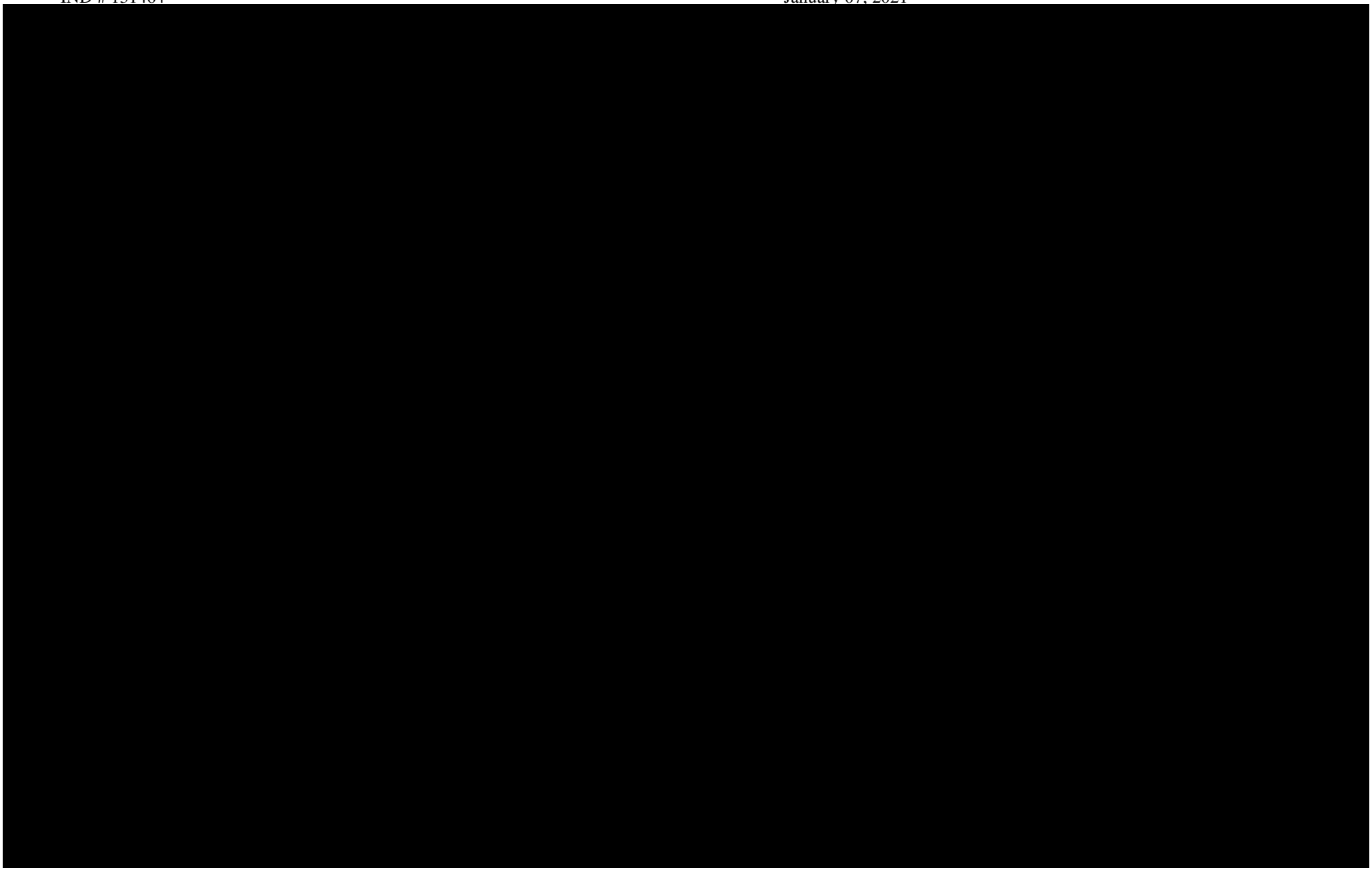
Truscott, R. J. (2009). "Presbyopia. Emerging from a blur towards an understanding of the molecular basis for this most common eye condition." Exp Eye Res **88**(2): 241-247.

Weller, M., H. Wilhelm, N. Sommer, J. Dichgans and H. Wietholter (1992). "Tonic pupil, areflexia, and segmental anhidrosis: two additional cases of Ross syndrome and review of the literature." J Neurol **239**(4): 231-234.

14 APPENDICES

Appendix 1: Schedule of Assessments





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Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

Appendix 3: Protocol Amendment Summary

AMENDMENT 1

BACKGROUND AND RATIONALE FOR AMENDMENT

The purpose of Protocol Amendment 1 is to:

1) correct Sponsor address
2) add / define at-home dosing windows
3) add / define windows for post-vehicle / post-treatment assessment timepoints
4) revise exclusion criteria #11 to remove 1-hour post-vehicle VA assessment.
5) revised exclusion criterias #5 & #6 to require the use of negative cylinder for assessment of inclusion
6) correct the numbering / formatting of exclusion criteria #17
7) update order of assessments/procedures in Section 8 to be corrected to note that selection of study eye and randomization occur before the first dose of study medication is instilled.
8) update the order of assessments in Section 8 and in Appendix 1: Schedule of Assessments, to note that the 40cm BDCVA assessment will be conducted after pupillometry and before the 4m distance and 4m low-luminance testing.
9) correct wording in Appendix 1, Section 11, Subject-Reported Drop Comfort Scale & Questionnaire, to accurately reflect when assessment is completed

SUMMARY OF CHANGES

In the table below, the protocol text was amended by the following conventions:

- Deletions to the original text are indicated by ~~strike through~~ letters.
- Additions to amended text are indicated by **bold** letters.
- Replacements of wording in the amended text are indicated by ***bold and italicized*** letters.

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[redacted]

[redacted]

[redacted]

[redacted]

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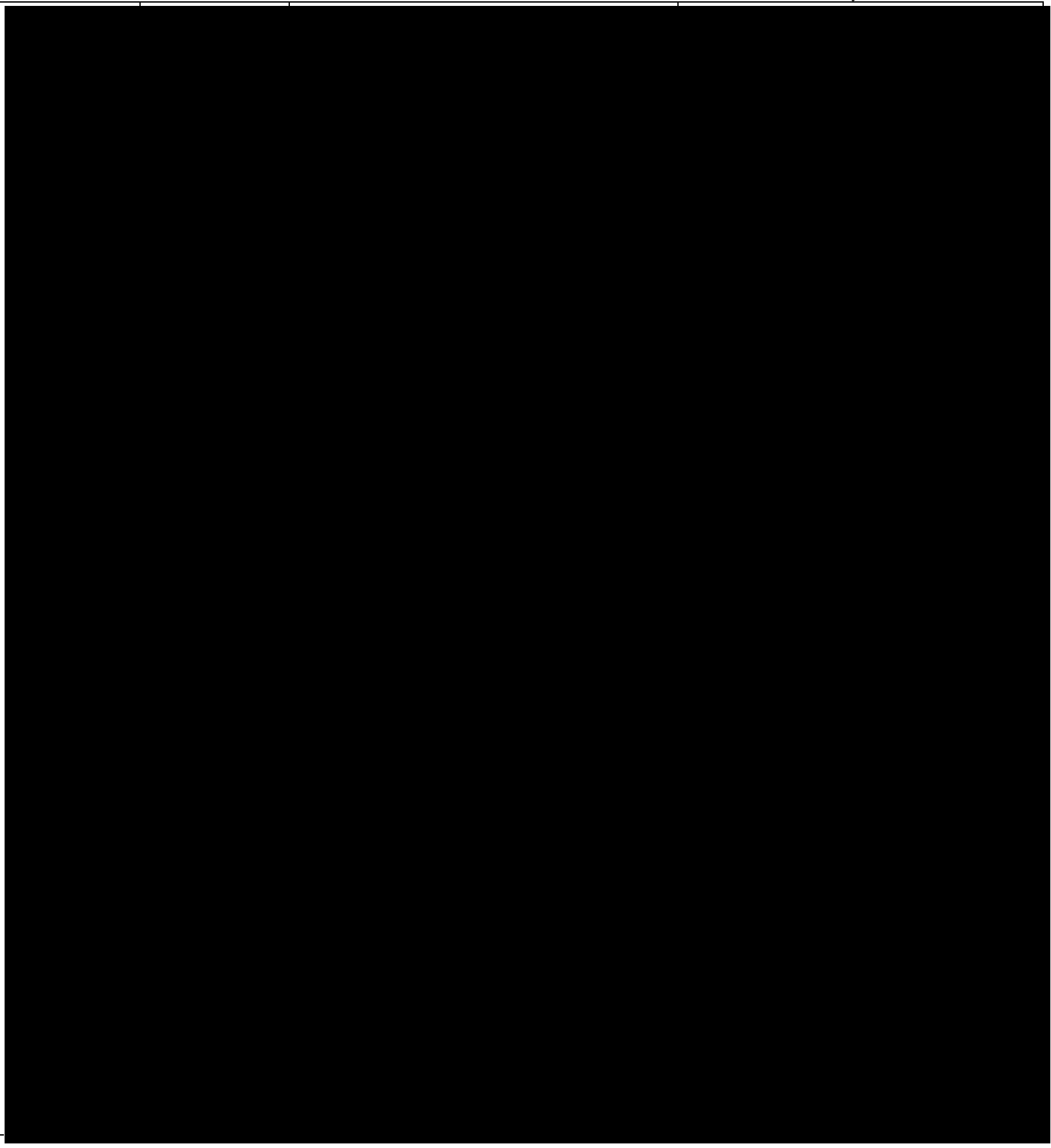

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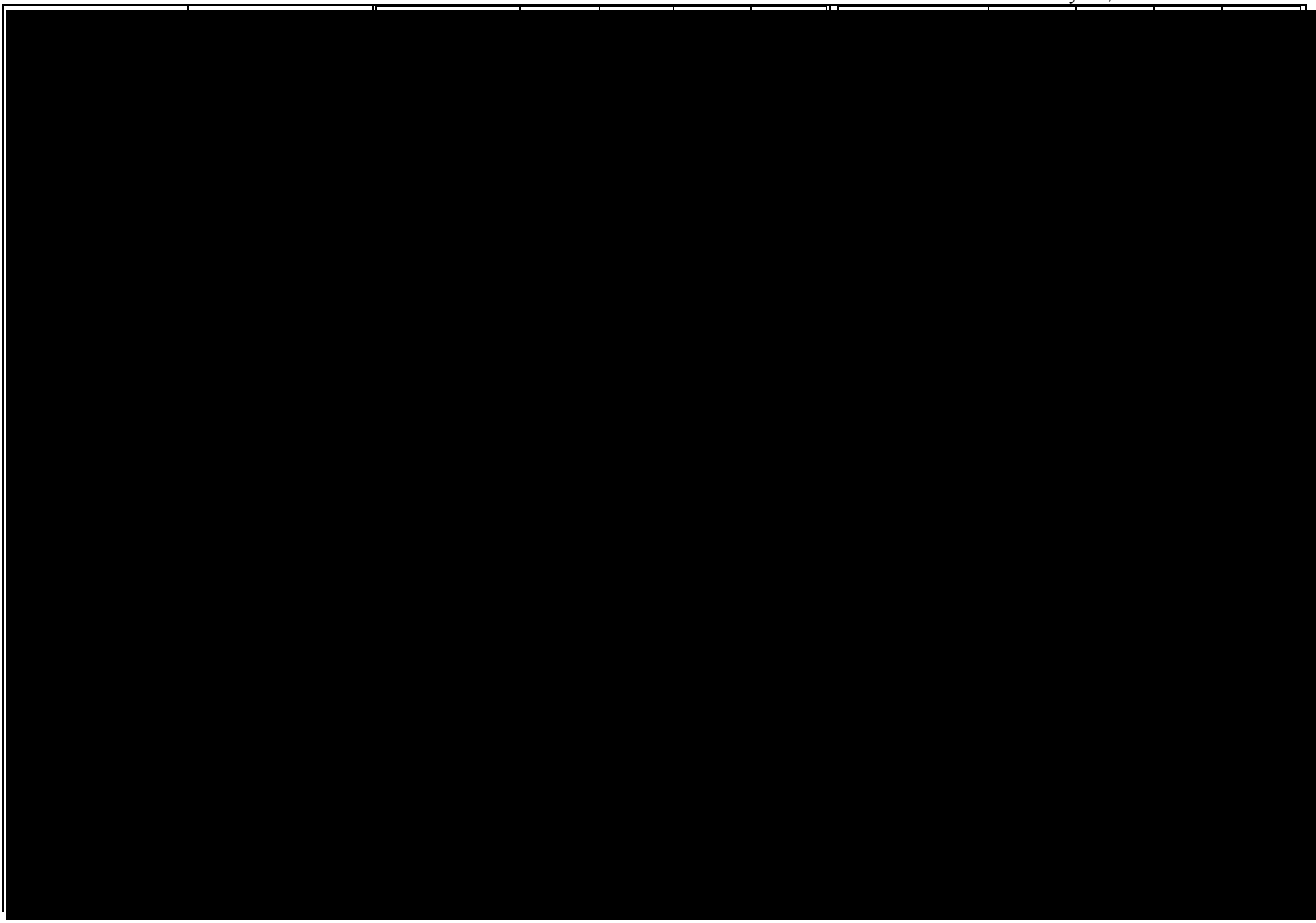

[redacted]

Appendix 4: Sponsor and [redacted] Approvals

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-2 study: Near Eye-vision Acuity Restoration)
Protocol Number:	20-150-0003

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Appendix 5: Investigator's Signature

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-2 study: Near Eye-vision Acuity Restoration)
Protocol Number:	20-150-0003

I agree to implement and conduct the study diligently and in strict compliance with the protocol, the Good Clinical Practice ICH E6 (R2) Guidance, and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the sponsor in confidence and, when this information is submitted to an institutional review board (IRB), ethical review committee or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

[Name]
Principal Investigator
[Affiliation]