CLINICAL TRIAL PROTOCOL CSF-1 SAFETY STUDY

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Safety of CSF-1 in Presbyopic Subjects
Protocol Number:	21-150-0005
Study Phase:	Phase 3
Investigational Product Name:	CSF-1 (pilocarpine hydrochloride 0.4% ophthalmic solution)
IND Number:	131464
Indication:	Presbyopia
Investigators:	Multi-center clinical investigation
Sponsor:	Orasis Pharmaceuticals, Ltd 6 Maskit St., P.O.B 12929 Herzliya 4673312, Israel +972 9 8877745
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:	December 17, 2021
Amendment 1:	April 7, 2022
Amendment 2:	September 20, 2022

Confidentiality Statement

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SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Safety of CSF-1 in Presbyopic Subjects
IND Number	131464
Protocol Number:	21-150-0005
Investigational Products:	CSF-1 (pilocarpine hydrochloride 0.4% ophthalmic solution) Placebo (Vehicle for CSF-1)
Study Phase:	Phase 3
Primary Objective:	To evaluate the safety of CSF-1 compared with vehicle in presbyopic subjects.
Secondary Objective:	Not applicable
Overall Study Design:	
Structure:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Safety of CSF-1 in Presbyopic Subjects
Duration:	At least 6 Weeks
Controls:	Vehicle Ophthalmic Solution (for CSF-1)
Dosage/Dose Regimen/ Instillation/Application/Use:	Enrolled subjects will be randomized 2:1 to receive CSF-1 or vehicle bilaterally. Subjects will be instructed to dose one drop in each eye, twice daily (BID), at 2 to 3 hours intervals (OU). This regimen should be followed daily.. Subjects who have not completed Visit 4 (Week 6) at the time of Protocol Amendment 2.0 approval will dose for at least 6 weeks. Subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will dose until the next scheduled visit and exit the study. Subjects must avoid dosing prior to visit on the day of a visit. If subjects dose prior to their visit, the study visit will be rescheduled.
Summary of Visit Schedule:	• Visit 1 (Day -30 to Day -7): Screening; • Visit 2 (Week 1/Day 1): Baseline Assessments; • Visit 3 (Week 2/Day 15 ± 2 days): Safety Assessments; • Visit 4 (Week 6 + 7 days): Safety Assessments & Exit; • Visit 5 (Week 12 ± 7 days): Safety Assessments & Exit Visit (for all subjects who have completed Visit 4 at the time of Protocol Amendment 2.0 approval) • Visit 6 (Week 18 ± 7 days): Safety Assessments & Exit Visit (for all subjects who have completed Visit 5 at the time of Protocol Amendment 2.0 approval) • Visit 7 (Week 21 ± 7 days): Safety Assessments & Exit Visit (for all subjects who have completed Visit 6 at the time of Protocol Amendment 2.0 approval)
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 potential of bias during data collection the evaluation of clinical endpoints.

	Randomization will be at a 2:1 ratio (CSF-1:Vehicle).
Study Population Characteristics:	
Number of Subjects:	This study will enroll approximately 170 subjects (approximately 113 subjects assigned to CSF-1 and approximately 57 subjects assigned to vehicle) treated for at least 6 weeks. All subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will exit the study at the next scheduled visit ([redacted]).
Condition/Disease:	Healthy adult subjects ages 40 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 comply with the study requirements and attend all study visits; 3. Be 40-64 years of age of either sex and any race or ethnicity and must be in general healthy condition at Visit 1; 4. [redacted] 6. Have a negative serum pregnancy test result at Visit 1, if female is 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; 7. Be able and willing to avoid all disallowed medications for the appropriate washout period and during the study without significant risk to the subject; 8. Have natural lens (phakic) in both eyes.
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 sensitivity to the use of any of the study medications or their components; 3. Have an active ocular infection at Visit 1 (bacterial, viral,

	or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (e.g., moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) in either eye; 4. [redacted] 5. [redacted] 6. Have any clinically significant abnormal findings on systemic labs (i.e., hematology, blood chemistry analysis, and urinalysis) at screening. If a laboratory finding is outside the normal limits, clinically significant abnormal findings will be determined by the investigator; 7. Have clinically significant abnormal findings (e.g., clinically significant cataract, central corneal scar) on a slit lamp biomicroscopy exam in either eye documented at screening/baseline or a known history of a clinically significant slit-lamp finding in either eye at visit 1; 8. Have intraocular pressure (IOP) that is [redacted] or have a prior diagnosis of ocular hypertension or glaucoma or currently being treated with any type of topical IOP lowering (glaucoma) medication at Visit 1; 9. Have any clinically significant abnormal findings on dilated indirect fundus exam in either eye at screening or undilated fundus exam at baseline or a known history of retinal detachment, retinal tears, or clinically significant retinal disease in either eye; 10. Have a known history or diagnosis in the past of iritis, scleritis, or uveitis, whether active or inactive; 11. Have had surgical intervention (ocular or systemic) within 1 year prior to Visit 1, or a planned surgical intervention within 30 days after the study exit visit; 12. [redacted] 13. Have completed participation in an investigational drug or device study within 30 days of Visit 1; 14. 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 not allowed): i. Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., Advil®, Motrin®) except for once daily Aspirin used in (cardiovascular) prophylactic dose of 81 mg. Topical NSAIDs are allowed;

	ii. narcotic (opiate class) pain medication (e.g., codeine, OxyContin®, Vicodin®, Tramadol®); b. Two (2) weeks (14 days) prior to Visit 1 and for the duration of the study: i. bladder medications (cholinergics [e.g., Urecholine®, bethanechol], anticholinergics [e.g., oxybutynin] and antimuscarinics [e.g., fesoterodine]); ii. attention-deficit/hyperactivity disorder (ADHD) medications c. During the year preceding the enrollment in the study and during the entire duration of the study: i. Any antipsychotics ii. Any antidepressants; 15. Have a diagnosis of unstable diabetes mellitus (i.e., A1C levels less than 4% or greater than 6%) or a history of elevated blood sugar as reported by the patient; 16. Have a condition or a situation, which, 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; 17. Have previously participated in CSF-1 clinical trial; 18. Be currently using any topical ophthalmic medications that may confound safety data (e.g., Vuity®, Latisse®, Upneeq®, Lumify®) and not be able to discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); the respective wash-out periods are required for the following medications: a. Latisse®, Upneeq®, Vuity®, and Lumify®: 14 days prior to Visit 1
Study Formulations:	• CSF-1; • Placebo (Vehicle)
Evaluation Criteria	
Safety Measures	1. Adverse events (AE) (reported, elicited, and observed) 2. BDCVA (best distance-corrected visual acuity) 3. Low-luminance BDCVA (LL-BDCVA) 4. Slit lamp biomicroscopy 5. Fluorescein staining 6. IOP 7. Undilated fundus exam at Visit 2 Baseline (Week 1/ Day 1) 8. Serum pregnancy test at Visit 1 Screening and Urine pregnancy test at Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time

	of Protocol Amendment 2.0 approval (for females of childbearing potential) 9. Physical examination at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval 10. Vital signs (resting blood pressure and pulse) at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval 11. Systemic labs: hematology, blood chemistry analysis, and urinalysis at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval 12. Dilated indirect fundus exam at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval

General Statistical Methods and Types of Analyses:

Analysis Set

Safety Set – The safety set will include all randomized subjects who have received at least 1 dose of the study drug. Subjects in the safety set will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

General Considerations

In general, quantitative/continuous data will be summarized using descriptive statistics (number of subjects [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 last measurement taken prior to the administration of the first dose of study drug. Change from baseline will be calculated as follow-up measure minus baseline measure.

Summaries and listings will be presented for all subjects, or safety set, as needed. Safety analyses will be conducted in the safety set.

Sample Size

Approximately 170 subjects treated will be randomized into the study in a 2:1 ratio of CSF-1:vehicle (approximately 113 randomized subjects assigned to CSF-1 and approximately 57 subjects assigned to vehicle) completing at least 6 weeks of treatment. Any subjects treated beyond Visit 4 (Week 6) at the time of Protocol Amendment 2.0 approval will exit the study at the next scheduled visit. All subject data will be analyzed.

A sample size of 113 subjects treated with CSF-1 for at least 6 weeks will have at least 95% probability of detecting adverse events that occur at a rate of 2.66% or greater.

Safety Analysis

All safety data will be analyzed using the safety set. Safety of CSF-1 compared to vehicle will be assessed by the review of all safety parameters.

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. A treatment-emergent adverse event (TEAE) is any event not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment. TEAEs will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. The number of AEs, TEAEs, serious TEAEs, and TEAEs causing premature

discontinuation will be provided by treatment group. In addition, the frequency and percentage of subjects with at least one AE, at least one TEAE, and at least one serious TEAE will also be provided by treatment group.

Similar summaries will also be presented for TEAEs related to the study drug, by severity, and by study day of onset. 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 each treatment group. Number of AEs by a set interval of time will be summarized for each interval. Or number of AEs will be summarized for set intervals of time..

Changes from baseline in BDCVA, LL-BDCVA, slit lamp biomicroscopy, fluorescein staining, IOP, and dilated indirect fundus examination will be summarized descriptively at each visit where performed by treatment group.

The categorical summaries for the loss of ≥ 0.2 logMAR from baseline (yes/no) and for the loss of > 0.2 logMAR (yes/no) in BDCVA and LL-BDCVA at each visit will also be presented and compared between treatment groups using Pearson chi-squared test or Fisher's exact test if any cell counts are less than 5.

[redacted]

Full details of the safety analyses will be specified in the formal Statistical Analysis Plan (SAP).

Summary of Known and Potential Risks and Benefits to Human Subjects

The safety and efficacy of CSF-1 (which was initially developed as a fixed dose combination (FDC) of pilocarpine HCl 0.2% or 0.4% and diclofenac 0.006%) 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 (as FDC).

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 and that the pilocarpine 0.4% strength showed a statistically significant ≥ 3-line improvement in monocular best corrected visual acuity (BCVA) at 40 cm from baseline, 1-hour post-treatment (p-value=0.0015 for CSF-1 (FDC) group and p-value= 0.0002 for pilocarpine HCl group) compared to the diclofenac group, demonstrating success for the primary efficacy endpoint.

In addition, a post-hoc analysis was conducted with the additional criteria of no loss of ≥ 5 letters in distance visual acuity (VA) to the primary endpoint. Results of this post-hoc analysis showed that 43.1% of the subjects in the FDC group, and 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 from baseline, 1-hour post-treatment. 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 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.

The initial formulation of CSF-1 was a fixed-dose combination (FDC), including 0.2% pilocarpine nitrate and 0.006% diclofenac sodium. A feasibility study and 2 clinical (Phase 2a) studies demonstrated acute miosis as well as favorable safety and efficacy, leading to the continued development of CSF-1 as an ophthalmic solution.

Post evaluation of Phase 2a study results, a Phase 2b study was conducted to determine 1) the contribution of each active ingredient of the study drug (pilocarpine HCl and diclofenac sodium) and 2) the impact of increasing pilocarpine HCl concentrations (0.2% versus 0.4%) on the efficacy of the study

drug for the treatment of presbyopia. Results of this study showed that both, CSF-1-FDC (pilocarpine HCl 0.4%/diclofenac sodium 0.006%) and pilocarpine HCl 0.4%, demonstrated statistically significant improvements in best distance-corrected visual acuity (BDCVA) scores at 40 cm compared to diclofenac alone 1-hour post-treatment, with neither formulation raising significant safety concerns. 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. Therefore, the selected active ingredient and strength for CSF-1 for the pivotal Phase 3 studies was pilocarpine HCl 0.4%. Both Phase 3 pivotal studies (NEAR-1 and NEAR-2) were recently successfully completed. All primary and key secondary endpoints (previously agreed with Food and Drug Administration [FDA]) were achieved in both studies. In addition, all safety parameters showed that CSF-1 is safe and well tolerated.

A human pharmacokinetic (PK) clinical trial was also completed. After repeated ocular dosing of CSF-1 ophthalmic solutions (2 doses daily, 2 hours apart, for 8 days), plasma pilocarpine concentrations were low (<1.5 ng/mL) but measurable at all evaluated post dose time points in all 15 subjects enrolled in the study. The study demonstrated the low systemic exposure of pilocarpine after 8 days of twice a day treatment with CSF-1.

1 TABLE OF CONTENTS

2 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 a day
CFR	Code of Federal Regulations
eCRF	electronic case report form
D	diopter
FDA	Food and Drug Administration
FDC	fixed dose combination
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	investigational new drug application
IOL	intraocular lens
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
IUD	intrauterine device
HCl	hydrochloric acid
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Information Portability and Accountability Act
LASEK	laser-assisted epithelial keratomileusis
LASIK	laser-assisted in-situ keratomileusis
LDPE	low-density polyethylene
LL-BDCVA	low-luminance best distance-corrected visual acuity
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MRSE	manifest refraction spherical equivalent
NSAID	non-steroidal anti-inflammatory drug
OTC	over-the-counter
PRK	photorefractive keratectomy

PT	preferred term
RGP	rigid gas permeable
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
USP	United States Pharmacopeia
VA	visual acuity

3 INTRODUCTION

Most individuals will develop symptoms of presbyopia by age 50 (Truscott 2009), and approximately 50% of the population with presbyopia does not have adequate corrective lenses, resulting in some level of disability when performing tasks requiring near visual acuity (VA) (Holden et al 2008). This resulted in a global burden of presbyopia exceeding 1.8 billion people in 2015 (Holden et al 2008), and prevalence is increasing. 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 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.

The neural mechanism of accommodation is the adjustment of the size of the pupil. Pupil size is determined by the dimensions of sphincter and dilator muscle spindles of the iris. The pupil becomes smaller when the eye accommodates. This reduction in the size of the pupil (termed miosis) improves the resolution of the retinal image by preventing diverging light rays hitting the periphery of the cornea and lens from reaching the retina. Miosis further increases the depth of field of the eye. A relatively small pupil offers increased depth of field in a way similar to that achieved by reducing the aperture of a camera.

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 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 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 et al. 2002) and a broad spectrum of systemic conditions including botulism (Monaco et al. 1998), leprosy (Lana-Peixoto et al. 2014), sarcoidosis (Bowie and Givre 2003), and Ross syndrome (Weller et al. 1992; Chemmanam et al. 2007).

Pupil size is determined by the dimensions of sphincter and dilator muscle spindles of the iris. Once the pupil constricts (an action termed miosis), it improves the resolution of the retinal image by preventing diverging light rays hitting the periphery of the cornea and lens, from reaching the retina. Miosis further increases the optical depth of field of the eye and is leading to better visual acuity of close objects. At high concentrations, pilocarpine drops applied to the ocular surface result in miosis but also stimulate an accommodative action that could blur distance vision if the individual eye has a crystalline lens that is sufficiently pliable. Throughout the development of CSF-1, Orasis found that pilocarpine HCl eye drops serially diluted down to as low as 0.4% concentrations still produce miosis, but without affecting distance visual acuity.

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

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 study and two Phase 2 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 only (0.006%), pilocarpine (0.2% and 0.4%) combined with diclofenac (0.006%), and pilocarpine only (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 showing a ≥ 3-line improvement in monocular best corrected visual acuity (BCVA) at 40 cm from baseline, 1- hour post-treatment was statistically significantly higher in the pilocarpine HCl 0.4%/diclofenac sodium 0.006% group and in the pilocarpine HCl 0.4% alone group (p-values=0.0015 and 0.0002 respectively) compared to the diclofenac group. 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.

Additionally, the safety results were similar between the 3 arms. For this reason, the Sponsor had decided to drop diclofenac from the CSF-1 clinical formulation, and to continue the CSF-1 clinical development with pilocarpine HCl 0.4% as the only active ingredient.

Two identical Phase 3, multicenter, randomized, double masked, placebo (vehicle) controlled, 2-arm, efficacy and safety studies (NEAR-1 and NEAR-2) were conducted with the current formulation of CSF-1 (pilocarpine HCl 0.4%) and were recently completed.

A total of 309 subjects with presbyopia were randomized in NEAR-1 (155 CSF-1 and 154 vehicle) and 304 were randomized in NEAR-2 (154 CSF-1 and 150 vehicle). Participants were treated BID (with an interval of 2 or 3 hours between both doses) with 1 drop of CSF-1 in each eye, for a period of 15 days. Efficacy parameters (Best Distance Corrected Visual Acuity (BDCVA) at 40cm and 4m, as well as pupil diameters) were measured on day 1, 8 and 15 at various time points during these days. The primary and key secondary end-points were the 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 4 m) in the study eye on Day 8, 1 hour post dose 1 (primary end-point) and on the same Day 8, up to 4h post dose 1. The other secondary endpoints were the same endpoints but measured on Day 1 (up to 6h post dose 1) and on Day 15 (up to 8h post dose 1).

In both NEAR-1 and NEAR-2 studies, CSF-1 showed a statistically significant superior effect compared to vehicle in all primary and key secondary endpoints (all time points on Day 8 [from 1 hour post-dose 1 to 2 hours post-dose 2]). The superiority of CSF-1 compared to vehicle, was also demonstrated on Day 1 and on Day 15. The pooled data of NEAR-1 and NEAR-2 showed a statistically significant superior effect in all time points on Day 1 and Day 15.

In both Phase 3 studies, the safety endpoints of Slit-Lamp Biomicroscopy, BDCVA, Intraocular Pressure, and Conjunctival Redness, changes from baseline were found to be comparable between the CSF-1 and vehicle groups. On a drop comfort scale from 0 (very comfortable) to 10 (very uncomfortable), mean scores were <2 at all timepoints, indicating that CSF-1 was well tolerated. [redacted]

The current safety study is initiated to evaluate the safety of CSF-1, administered twice a day (BID) with an interval of 2-3 hours.

4 STUDY OBJECTIVE

4.1 Primary Objective

The primary objective of the study is to evaluate the safety of CSF-1 compared with vehicle in presbyopic subjects.

4.2 Study Hypothesis

CSF-1 ophthalmic solution (0.4% pilocarpine hydrochloride) has an acceptable safety profile when used in healthy adults with a history of presbyopia.

5 OVERALL STUDY DESIGN

This is a 4 visit, multi-center, double-masked, vehicle-controlled study evaluating the long -term safety of CSF-1 compared to vehicle in a total of approximately 170 subjects with presbyopia (approximately 113 subjects assigned to CSF-1 and approximately 57 subjects [redacted] All subjects who have not completed Visit 4 at the time of Protocol Amendment 2.0 approval will proceed with the scheduled visits until study exit at Visit 4 (Week 6). All subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval [redacted] will proceed to study exit at the next scheduled study visit ([redacted]). The maximum timepoint for these subjects to exit the study will be Visit 7 (Week 21). All subject data will be analyzed for all measured timepoints, including data from subjects treated beyond Visit 4.

Subjects will be consented and study eligibility will be determined at Visit 1 (Screening). Subjects who remain eligible after Visit 1 will return for Visit 2 (Baseline Visit) to be assessed for randomization into the study. If eligible, subjects will be enrolled in this safety study and randomized 2:1 to receive CSF-1 or vehicle bilaterally. All study treatments are topical ophthalmic solutions that should be administered bilaterally. The initial dose will be instilled during Visit 2 after completing the visual acuity assessment. Subjects will be instructed to instill with a single drop in each eye (OU) twice daily (BID) at approximately 2-to-3-hour intervals later. Subjects would be reminded not to dose at home on clinic visit days. Medical history updates and adverse event assessments will be done at this and subsequent visits. Investigational product and dosing diary will be dispensed to subject. Subject will be instructed to return to clinic at the next scheduled visit.

5.1 Dose Regimen

Enrolled subjects will be randomized 2:1 to receive CSF-1 or vehicle bilaterally. Subjects will be instructed to dose one drop in each eye, twice daily (BID), at 2 to 3 hours intervals (OU). This regimen should be followed daily. Subjects who have not completed Visit 4 (Week 6) at the time of Protocol Amendment 2.0 approval will dose for at least 6 weeks. Subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will dose until the next scheduled visit ([redacted]) and exit the study. Subjects must avoid dosing prior to visit on the day of a visit. If subjects dose prior to their visit, the study visit will be rescheduled.

6 STUDY POPULATION

6.1 Number of Subjects

This study will enroll approximately 170 subjects (approximately 113 subjects assigned to CSF-1 and approximately 57 subjects assigned to vehicle) into the trial.

All subjects who have not completed Visit 4 (Week 6) at the time of Protocol Amendment 2.0 approval will be treated for at least 6 weeks and complete 4 study visits. All subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will continue to be treated and exit the study at the next scheduled visit.

6.2 Study Population Characteristics

The study will include healthy adult subjects between 40 and 64 years of age with presbyopia who do not have any conditions, in the investigator's opinion, that may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

6.3 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 comply with the study requirements and attend all study visits;
3. Be 40-64 years of age of either sex and any race or ethnicity and must be in general healthy condition at Visit 1;
4. [redacted]
5. [redacted]
6. Have a negative serum pregnancy test result at Visit 1, if female is 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;

7. Be able and willing to avoid all disallowed medications for the appropriate washout period and during the study without significant risk to the subject;
8. Have natural lens (phakic) in both eyes.

6.4 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 sensitivity to the use of any of the study medications or their components;
3. Have an active ocular infection at Visit 1 (bacterial, viral, or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (e.g., moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) in either eye;
4. [redacted]
5. [redacted]
6. Have any clinically significant abnormal findings on systemic labs (i.e., hematology, blood chemistry analysis, and urinalysis) at screening. If a laboratory finding is outside the normal limits, clinically significant abnormal findings will be determined by the investigator.
7. Have clinically significant abnormal findings (e.g., clinically significant cataract, central corneal scar) on a slit lamp biomicroscopy exam in either eye documented at screening/baseline or a known history of a clinically significant slit-lamp finding in either eye at Visit 1;
8. Have intraocular pressure (IOP) [redacted] or have a prior diagnosis of ocular hypertension or glaucoma or currently being treated with any type of topical IOP lowering (glaucoma) medication at Visit 1;
9. Have any clinically significant abnormal findings on dilated indirect fundus exam in either eye at screening or undilated fundus exam in either eye at baseline or a known history of retinal detachment, retinal tears, or clinically significant retinal disease in either eye;

10. Have a known history or diagnosis in the past of: iritis, scleritis, or uveitis, whether active or inactive;
11. Have had surgical intervention (ocular or systemic) within 1 year prior to Visit 1, or a planned surgical intervention within 30 days after the study exit visit;
12. [redacted]
13. Have completed participation in an investigational drug or device study within 30 days of Visit 1;
14. 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 not allowed):
        i. Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., Advil®, Motrin®) except for once daily Aspirin used in (cardiovascular) prophylactic dose of 81 mg. Topical NSAIDs are allowed.
        ii. narcotic (opiate class) pain medication (e.g., codeine, OxyContin®, Vicodin®, Tramadol®)
    b) Two (2) weeks (14 days) prior to Visit 1 and for the duration of the study:
        i. bladder medications (cholinergics [e.g., Urecholine®, bethanechol], anticholinergics [e.g., oxybutynin] and antimuscarinics [e.g., fesoterodine])
        ii. attention-deficit/hyperactivity disorder (ADHD) medications
    c) During the year preceding the enrollment in the study and during the entire duration of the study:
        i. Any antipsychotics
        ii. Any antidepressants
15. Have a diagnosis of unstable diabetes mellitus (i.e., A1C levels less than 4% or greater than 6%) or a history of elevated blood sugar as reported by the patient;
16. Have a condition or a situation, which, 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.
17. Have previously participated in CSF-1 clinical trial;
18. Be currently using any topical ophthalmic medications that may confound safety data (e.g., Vuity®, Latisse®, Upneeq®, Lumify®) and not be able to discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); the respective wash-out periods are required for

the following medications:

a) Latisse®, Upneeq®, Vuity®, and Lumify®: 14 days prior to Visit 1

6.5 Withdrawal Criteria

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 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 any visit in either eye.
- Subjects may also be withdrawn from the study for the following reasons:
    - Adverse event (AE)
    - Lost to follow-up
    - Withdrawal of consent by subject
    - Investigator's discretion
    - Death
    - Subject not adequately following required study procedures
    - Study terminated by the Sponsor
    - Other

Subject withdrawals will be documented on the subject's source document.

7 STUDY PARAMETERS

7.1 Safety Measures

Safety will be assessed by the following measures for all subjects:

- Adverse events (AE) (reported, elicited, and observed)
- BDCVA (best distance-corrected visual acuity)
- Low-luminance BDCVA (LL-BDCVA)
- Slit lamp biomicroscopy
- Fluorescein staining
- IOP
- Undilated fundus exam at Visit 2 Baseline (Week 1/ Day 1)

[redacted]

- Serum pregnancy test at Visit 1 Screening and Urine pregnancy test at Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval (for females of childbearing potential)
- Physical examination at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval
- Vital signs (resting blood pressure and pulse) at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval
- Systemic labs: hematology, blood chemistry analysis, and urinalysis at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval
- Dilated indirect fundus exam at Visit 1 Screening and Visit 4 (Week 6) or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval

8 STUDY MATERIALS

8.1 Study treatments

The investigational product (IP) is CSF-1.

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 pharmacopeial 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 CSF-1 and vehicle are packaged in single-dose transparent low-density polyethylene (LDPE) vials, enclosed within a pouch. Each pouch includes five vials. CSF-1 will be evaluated for comparison to vehicle.

8.1.1 Instructions for Use and Administration

CSF-1 or vehicle are topical ophthalmic solutions that should be administered bilaterally. Subjects will be instructed to instill with a single drop in each eye twice daily (BID). The first daily dose should occur in the morning, with the second dose following approximately 2 to 3 hours later. Subjects should be reminded not to dose at home on clinic visit days.

8.1.2 Subject Instructions

After obtaining written informed consent, Subjects will be screened at Visit 1. At Visit 2 subjects will be randomized and will receive study drug and a paper dosing diary.

Subjects will be instructed to instill a single drop of study drug in each eye twice daily (BID). The first daily dose should occur in the morning, with the second dose following approximately 2 to 3 hours later and subjects should record each dosing time in their diary.

Subjects should not dose on the AM of each visit. At each visit, subjects will receive their AM dose at the visit by study personnel after their visual assessments are completed.

Subjects will be instructed that study drug must be stored in a refrigerator between 2° to 8°C (36° to 46°F). An open vial should never be re-used. Subjects will be instructed to save all used vials and return all used vials and unused study drug kits to next study visit for a compliance check.

At Visit 4 or the next scheduled study visit, subjects will return to clinic to complete exit visit assessments. Study drug (used and unused vials) and diary will be collected from all subjects. All subjects who have not completed Visit 4 (Week 6) at the time of Protocol Amendment 2.0 approval will exit the study after all assessments are complete at Visit 4. All subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will exit the study after all assessments are complete at the next scheduled visit ([redacted]).

9 STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the criteria in Section 6.3 and Section 6.4 will be considered for entry into this study.

9.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or commencement of study related procedures), the study will be discussed with each subject. Subjects wishing to participate must provide written informed consent signing and dating an informed consent form (ICF) and other written documentation in accordance with local privacy requirements (where applicable).

9.1.3 Washout Intervals

There are no washout intervals for this study.

9.1.4 Procedures for Final Study Entry

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

9.1.5 Pregnancy

Females must have a negative serum pregnancy test result 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 result at any visit following Visit 1, the Investigator will inform [redacted] and the sponsor about the positive pregnancy test result

within 24 hours of the time the pregnancy was reported to the Investigator, regardless of whether an AE/SAE (serious adverse event) was reported.

9.1.6 Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a subject number (a five-digit number starting with the 2-digit site number followed by a sequential three-digit number assigned as xx-201). Once a subject meets all qualification criteria at Visit 2, he/she will be randomized in a 2:1 ratio via an interactive response technology system to 1 of 2 treatment groups (CSF-1 or CSF-1 vehicle), and stratified by Cohort, iris color (dark versus light [i.e., blue, green, gray, and hazel]) and by baseline manifest refraction spherical equivalent (-4.5 Diopter (D) to <-0.5 D, -0.5 D to +0.75 D, and >+0.75 D to +2.0 D).

As there is no designated study eye, the worst eye as defined by the BDCVA score at Visit 1 will be used to determine the eye for manifest refraction which is used for stratification. If both eyes have the same BDCVA score, the right eye will be selected for manifest refraction which is used for stratification. Randomization will not be stratified by site.

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.

This study will include approximately 170 subjects (approximately 113 randomized subjects assigned to CSF-1 and approximately 57 subjects assigned to vehicle) treated for at least 6 weeks. Any subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will exit the study at the next scheduled visit ([redacted]).

9.2 Concurrent Therapies and Medical History

The use of any concurrent medication, prescription, or over-the-counter (OTC) medication taken within 30 days of Visit 1, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

All significant current and relevant ocular and non-ocular medical and surgical history is to be recorded on the subject's source document and corresponding eCRF. Any significant general and surgical health history should be recorded on the subject's source documents.

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

9.2.1 Prohibited Medications/Treatments

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.

Also, the following medications are prohibited 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 not allowed):

i. nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., Advil®, Motrin®) except for once daily Aspirin used in (cardiovascular) prophylactic dose of 81 mg. Topical NSAIDs are allowed.

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 medications [cholinergics (e.g., Urecholine®, bethanechol), anticholinergics (e.g., oxybutynin) and antimuscarinics (e.g., fesoterodine)]

ii. attention-deficit/hyperactivity disorder (ADHD) medications

iii. Latisse®, Upneeq®, Vuity®, and Lumify®

c. During the year preceding the enrollment in the study and during the entire duration of the study:

i. Any antipsychotics

ii. Any antidepressants

9.3 Examination Procedures

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

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

9.3.1.1 Visit 1 (Day -30 to Day -7): Screening

[redacted]

9.3.1.2 Visit 2 (Week 1/Day 1): Baseline Assessments

[redacted]

9.3.1.3 Visit 3 (Week 2/Day 15 ± 2 days): Safety Assessments

[redacted]

9.3.1.4 Visit 4 (Week 6 + 7 days): Safety Assessments & Exit Visit (for all subjects who have not completed Visit 4 at the time of Protocol Amendment 2.0 approval)

[redacted]

[redacted]

9.3.1.5 Visit 5 (Week 12 ± 7 days): Safety Assessments & Exit Visit (for all subjects who have completed Visit 4 at the time of Protocol Amendment 2.0 approval)

[redacted]

9.3.1.6 Visit 6 (Week 18 ± 7 days): Safety Assessments & Exit Visit (for all subjects who have completed Visit 5 at the time of Protocol Amendment 2.0 approval)

[redacted]

9.3.1.7 Visit 7 (Week 21 ± 7 days): Safety Assessments & Exit Visit (for all subjects who have completed Visit 6 at the time of Protocol Amendment 2.0 approval)

[redacted]

[redacted]

9.4 Schedule of Visits, Measurements and Dosing

9.4.1 Scheduled Visit

Refer to [redacted] for a schedule of measurements at each visit.

9.4.2 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.

9.5 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 Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (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.

9.6 Subject Disposition

9.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

9.6.2 Withdrawn Subjects

A subject may be withdrawn for meeting any of the withdrawal criteria as described in Section 6.5.

9.6.3 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 10.0.

9.7 Study Termination

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

9.8 Study Duration

This study is comprised of up to 4 visits over a total duration of approximately 6 weeks. All subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will exit the study at the next scheduled visit ([redacted]).

9.9 Monitoring and Data Quality Assurance

During the course of the study a qualified study monitor will make routine site visits to review protocol compliance, assess IP accountability, and ensure the study is being conducted according to the pertinent regulatory requirements.

Prior to the start of the study, investigator and study site personnel are trained on protocol, CRFs, regulatory obligations and other relevant materials to conduct the study. The study monitor will determine compliance and take corrective action when necessary. Details of the study monitoring are outlined in a monitoring plan.

9.10 Auditing Procedures

Regulatory or ethics authorities of domestic and foreign agencies, Sponsor QA and [redacted], Inc. Quality Assurance and/or its designees may carry out on-site inspections and/or audits to evaluate compliance with the protocol and GCP principles. Access to the original source data may 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.

If an inspection is requested by a regulatory authority or IRB/EC, the investigator must inform the sponsor and [redacted] immediately of the request.

10 ADVERSE EVENTS

10.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease with onset following the signing of informed consent through study exit, that is 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.

An AE can also include a progression/worsening of an underlying disease, hypersensitivity and extravasation. Any clinically relevant deterioration in clinical findings 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 or diagnosis.

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 subject upon indirect

questioning.

At the time of informed consent, a subject's current and relevant medical history will be collected. At subsequent visits through the study exit visit, any AEs that are new and AEs (or Medical History events) that have worsening will collect severity and date of onset. Additionally, all AEs will be reviewed for dates of resolution, when applicable.

10.1.1 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.

10.1.2 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.

10.1.3 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 the 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 medical monitor will review and determine the expectedness of any serious adverse event (SAE) following the investigator's assessment. The final classification of an AE is subject to the sponsor's determination.

10.2 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: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., intra-ocular 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.

10.3 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.

10.3.1 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.

10.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, 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. 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 a SAE must be followed-up with and the outcome reported.

In the event of a SAE, the investigator must notify the study Medical Monitor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide [redacted] and the study sponsor with 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; and inform the IRB of the AE within their guidelines for reporting SAEs.

10.4 Procedures for Unmasking

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject.

In an emergency situation, where knowledge of the study drug treatment is critical to the study safety, the code may be broken. Study Treatment should remain masked to the CRO, study monitor (CRA) and Sponsor.

The Investigator should determine if the situation is a medical emergency (ocular or non-ocular) and whether the knowledge of the treatment is critical to subject safety. The Investigator should attempt to contact the Medical Monitor prior to unmasking the study treatment if possible. If unmasking is necessary, only the Primary Investigator will have the appropriate level of access in order to perform the unmasking within the [redacted] Clinical One Interactive Response Technology (IRT) System. The Primary Investigator will select the subject, follow the prompts to "Manage Subject" and then select the "Code Break" option. During this process, the Primary Investigator will be asked to confirm each step as well as whether the unmasking is related to an adverse event. Once all confirmatory questions are answered, the subject's treatment arm will be unblinded and the treatment arm will be displayed for the subject along with the assigned kits. For step-by-step details on Emergency Unmasking procedures, please refer to the IRT Training Plan.

The investigator must notify the Medical Monitor and the Study Monitor as soon as possible after unmasking. In addition, the Investigator must record the date, time and

reason for unmasking the study drug treatment in the source documentation, however, the subject treatment must NOT be recorded in the source documents. The unmasked subject must be discontinued from study.

10.5 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 subject's 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 a 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.

11 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 General Considerations

In general, quantitative/continuous data will be summarized using descriptive statistics (number of subjects [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 last measurement taken prior to the administration of the first dose of study drug. Change from baseline will be calculated as follow-up measure minus baseline measure.

Summaries and listings will be presented for all subjects, or safety set, as needed. Safety analyses will be conducted in the safety set.

11.2 Analysis Sets

- Safety Set – The safety set will include all randomized subjects who have received at least 1 dose of the study drug. Subjects in the safety set will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.
- Unit of Analysis

Both eyes will be displayed and analyzed for all ophthalmic safety variables.

11.3 Safety Endpoints

The safety endpoints are:

- AEs (reported, elicited, and observed)

- Vital signs (resting blood pressure and pulse) at Visit 1 Screening and Visit 4 - Week 6 or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval
- Physical exam (general health, head, eyes, ears, nose, throat, and other comments) at Visit 1 Screening, Visit 4 - Week 6 or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval
- BDCVA
- LL-BDCVA
- Slit lamp biomicroscopy
- Fluorescein staining
- IOP
- Dilated indirect fundus exam at Visit 1 Screening, Visit 4 - Week 6 or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval

Systemic labs at Visit 1 Screening, Visit 4 - Week 6 or next scheduled visit (study exit) for subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval [redacted]

11.4 Sample Size

Approximately 170 subjects will be randomized into the study in a 2:1 ratio of CSF-1:vehicle [approximately 113 randomized subjects assigned to CSF-1 and approximately 57 subjects randomized to vehicle] completing at least 6 weeks of treatment. Any subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval will exit the study at the next scheduled visit. All subject data will be analyzed.

[redacted]

11.5 Demographic and Baseline Characteristics

Subject demographics including age, gender, race, ethnicity, and iris color will be presented using continuous/categorical summary statistics as appropriate.

11.6 Safety Analysis

All safety data will be analyzed using the safety set. Safety of CSF-1 compared to vehicle will be assessed by the review of all safety parameters.

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) is defined as any event not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment. TEAEs will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. The

number of AEs, TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. In addition, the frequency and percentage of subjects with at least one AE, at least one TEAE, and at least one serious TEAE will also be provided by treatment group.

Similar summaries will also be presented for TEAEs related to the study drug, by severity, and by study day of onset. 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 each treatment group. The number of AEs as well as the incidence rate over the study period will also be summarized.

Changes from baseline in vital signs, BDCVA, LL-BDCVA, slit lamp biomicroscopy, IOP, and dilated indirect fundus examination and endothelial cell density will be summarized descriptively for at each visit by treatment group. Changes from baseline in endothelial cell density parameters will be tested between treatment groups using two-sample t-tests.

The categorical summaries for the loss of ≥ 0.2 logMAR from baseline (yes/no) and for the loss of > 0.2 logMAR (yes/no) in BDCVA and LL-BDCVA at each visit will also be presented and compared between treatment groups using Pearson chi-squared test or Fisher's exact test if any cell counts are less than 5.

Full details of the safety analyses will be specified in the formal Statistical Analysis Plan.

[redacted]

11.8 Missing Data

There will be no imputations for missing data.

11.9 Adjustment for Multiplicity

There will be no adjustments for multiplicity.

12 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 IPs in the countries involved will be adhered to.

12.1 Protection of Human Subjects

12.1.1 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

subject's 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.

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.

12.1.2 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.

12.2 Ethical Conduct of the Study

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

12.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and their 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 subject's 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 IP may ultimately be marketed in, but the subject's identity will not be disclosed in these documents.

12.4 Documentation

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

12.4.1 Retention of Documentation

All study-related correspondence, subject records, consent forms, records of the

distribution and use of all IPs, 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 IP. 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.

12.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

12.5.1 Labeling/Packaging

The study drug will be packaged into clinical kits and labeled. Each subject will be assigned bi-weekly kits over the course of the study. Each kit will be comprised of pouches and each pouch will contain one strip of 5 vials containing IP or vehicle. Each kit will be uniquely identified by a kit number. Kit labels will also include a space for the site to enter each subject's number and initials upon kit assignment. Clinical label texts for the packaging will meet applicable regulatory requirements.

12.5.2 Storage of Investigational Product

Study drug and Vehicle 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 or study drug manual for additional information.

12.5.3 Accountability of Investigational Product

For in-office dosing, the study drug is to be self-administered by the subject under the supervision of study site personnel and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified under this protocol to receive study drug.

The investigator 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.

12.5.4 Return or Disposal of Investigational Product

All IPs 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 subjects at Visit 4 or the next scheduled visit for those subjects treated beyond Visit 4 at the time of Protocol Amendment 2.0 approval before study exit.

12.6 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 subject's 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.

12.7 Handling of Biological Specimens

Not applicable.

12.8 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

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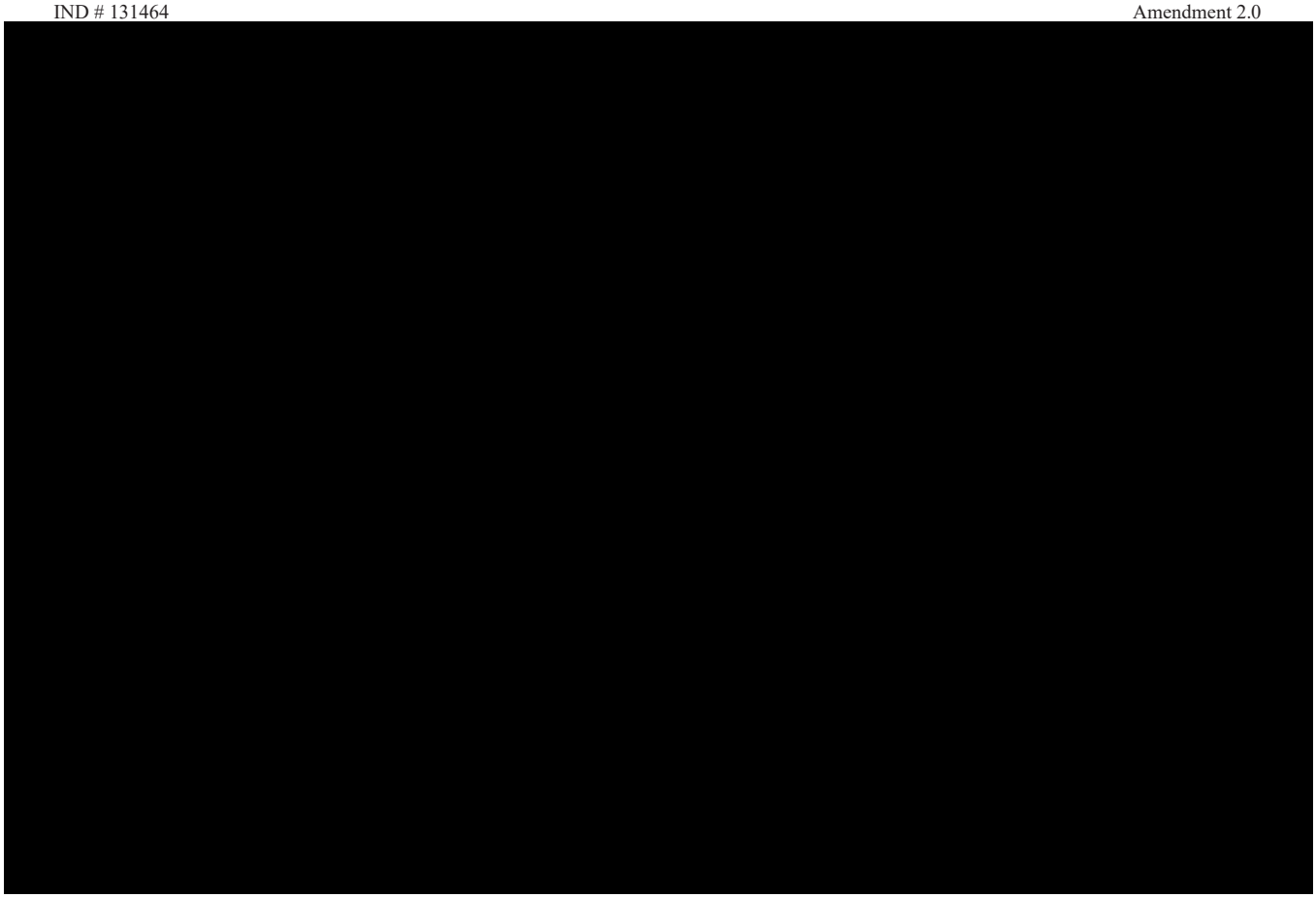
Weller, M., H. Wilhelm, N. Sommer, J. Dichgans and H. Wietholter (1992). "Tonic pupil, areflexia, and segmental anhidrosis: two additional cases of Ross syndrome and review of the literature." J Neurol **239**(4): 231-234.

14 APPENDICES

14.1 Appendix 1: Schedule of Visits and Measurements



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

14.3 Appendix 3: Sponsor [redacted] Approvals

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Safety of CSF-1 in Presbyopic Subjects
Protocol Number:	21-150-0005, Amendment 2
Final Date:	September 20, 2022

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.

[redacted]

09/20/2022

_____ Date:_____

09/20/2022

_____ Date:_____

09/20/2022

_____ Date:_____

09/20/2022

_____ Date:_____

[redacted]

[redacted]

09/20/2022

___ Date:_____

14.4 Appendix 4: Investigator's Signature

Protocol Title:	A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Safety of CSF-1 in Presbyopic Subjects
Protocol Number:	21-150-0005, Amendment 2
Final Date:	September 20, 2022

I agree to implement and conduct the study diligently and in strict compliance with the protocol, Good Clinical Practices 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]

14.5 Appendix 5: Protocol Amendment Summary

[redacted]