CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217836Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of NDA 217-836

Application Type	NDA
Application Number(s)	217836
Priority or Standard	Standard
Submit Date(s)	12/22/22
Received Date(s)	12/22/22
PDUFA Goal Date	10/22/23
Division/Office	Division of Ophthalmology/Office of Specialty Medicine (DO/OSM)
Reviewer Name(s)	Jenna M. Hammer, MD
Review Completion Date	See DARRTS Signature Date
Established/Proper Name	pilocarpine hydrochloride ophthalmic solution 0.4%
(Proposed) Trade Name	Qlosi
Applicant	Orasis Pharmaceuticals, Ltd.
Dosage Form(s)	Topical Solution
Applicant Proposed Dosing Regimen(s)	One drop OU bid
Applicant Proposed Indication(s)/Population(s)	Treatment of presbyopia in adults
Recommendation on Regulatory Action	Recommend Approval

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act

GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary / Product Introduction

Pilocarpine hydrochloride is a cholinergic muscarinic agonist that activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. Pilocarpine HCl 0.4% contracts the iris sphincter muscle therefore constricting the pupil to improve near visual acuity while maintaining some pupillary response to light. Pilocarpine hydrochloride ophthalmic solution 0.4% also contracts the ciliary muscle potentially shifting the eye to a more myopic state.

The Applicant has submitted as a 505(b)(1) application for Qlosi (pilocarpine hydrocholoride ophthalmic solution) 0.4% for the treatment of presbyopia in adults. The application references Salagen NDA 20237 for nonclinical toxicology reports, as well as clinical pharmacokinetic (PK) and clinical long-term safety studies conducted with an oral pilocarpine HCl product. The holder of NDA 20237, Concordia Pharmaceuticals Inc., has provided a letter of authorization (LOA) for Orasis Pharmaceuticals, Ltd. (Orasis) to reference and rely on the Salagen NDA.

This product may be alternately referred to as CSF-1 ophthalmic solution throughout this review.

1.1. Conclusions on the Substantial Evidence of Effectiveness

NDA 217836 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the safe and effective use of Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4% for the treatment of presbyopia in adults.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment
The data contained in this submission establishes that administration of Qlosi (pilocarpine hydrocholoride ophthalmic solution) 0.4% OU bid temporarily improves presbyopia in adults. Studies NEAR 1 (20-150-0002) and NEAR 2 (20-150-0003) demonstrate the ability of Qlosi (pilocarpine hydrocholoride ophthalmic solution) 0.4% to temporarily improve presbyopia have a three-line gain in near vision without losing more than one line of distance vision. The most common ocular adverse events for pilocarpine at > 5% are headache and instillation site pain. The benefit of pilocarpine hydrochloride ophthalmic solution 0.4% OU bid in treating patients with presbyopia outweighs the risks to patients with presbyopia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age. Both non-surgical (reading glasses, pilocarpine 1.25%) and surgical methods (i.e., IOL exchange) for the correction of presbyopia are available.	Without the use of pilocarpine or reading glasses older patients will have difficulty reading small text or doing activities (e.g., sewing) at close proximity.
Current Treatment Options	The current standard of care is use of refractive correction, i.e., reading glasses. Vuity, pilocarpine hydrochloride ophthalmic solution 1.25%, was approved 10/18/21, for the treatment of presbyopia in adults in a multi-use dropper bottle.	Will give patients an option of non-invasive, reversible, pharmacologic treatment for presbyopia, in preservative-free single-use vials.
Benefit	Will provide another treatment option for presbyopia.	Will give patients an option of non-invasive, reversible, pharmacologic treatment for presbyopia, in preservative-free single-use vials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Labeling will identify the expected adverse reactions. Pilocarpine risks are well known.	Pilocarpine in concentrations from 0.5% though 8% have been marketed for decades. Routine monitoring and reporting of all adverse events are expected to be adequate.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age. In 2005, 1.044 billion people globally were estimated to have presbyopia, and prevalence is expected to increase to 1.782 billion by 2050 (Holden 2008).

The exact cause of presbyopia is not known. The most likely cause of progressive presbyopia is a loss of elasticity of the crystalline lens, although changes in the lens's curvature from continual growth and loss of power of the ciliary muscles have also been postulated to contribute to its pathogenesis. The ability to focus on near objects declines throughout life, from an accommodation of about 20 D (ability to focus at 50 mm away) in a child, to 10 D at age 25 years (100 mm), and plateaus at 0.5 to 1 D at age 60 years (ability to focus down to 1 to 2 meters only). The first signs of presbyopia are usually first noticed between the ages of 40 and 50 years. Uncorrected near-vision impairment caused by presbyopia may have a negative impact on activities of daily living, career options, and self-esteem.

2.2. Analysis of Current Treatment Options

Both non-surgical and surgical methods for the correction of presbyopia are available. Traditional non-surgical methods of refractive correction for presbyopia include the use of dedicated reading spectacles, bifocal or multifocal spectacles, and monovision or multifocal contact lenses. Vuity, pilocarpine hydrochloride ophthalmic solution 1.25%, was approved in October 2021, for the treatment of presbyopia in adults and is considered safe and effective. It is currently approved to be dosed one drop OU daily. A second dose (one additional drop in each eye) may be administered 3 - 6 hours after the first dose. Vuity is supplied in a multi-use bottle.

A number of surgical techniques are also used for the treatment of presbyopia, which include monovision PRK or LASIK, conductive keratoplasty, intraocular lenses, and corneal inlays. However, for each of the existing technologies mentioned above, visual quality is reduced at one or more viewing distances (near, 40 cm; intermediate, 66 cm; distance, 4 m or more) and each comes with its own unique safety risks and complications. Commonly used reading glasses help with near vision but reduce vision at all other distances. Bifocals and progressive lenses (i.e., glasses, contacts) produce optical aberrations especially at intermediate distances, may compromise intermediate vision, and can increase the risk of falls. Multifocal optics reduce image quality uniformly at all viewing distances. The widespread number of surgical technologies is limited due to surgical risks, the need for repositioning, explanation, or regression of effect.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4% is not approved in the US or in any foreign market.

Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25%, was approved in October 2021 for the treatment of presbyopia in adults. Other pilocarpine products (i.e., Salagen NDA 20-237 and IsoptoCarpine NDA 200890 [1%, 2% and 4%]) are currently approved by the FDA. Salagen (pilocarpine hydrochloride) Tablets is indicated for xerostomia (dry mouth). IsoptoCarpine (pilocarpine hydrochloride ophthalmic solution) is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, the management of acute-angle closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and induction of miosis. The concentration of Isopto Carpine approved for reduction of IOP is 1% to 4% (1 drop administered to affected eye(s) up to 4 times daily).

The pharmacological mechanism for the treatment of presbyopia is believed to be related to pupillary constriction.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant (b) (4) The applicant conducted three Phase 2 studies (Studies FG-PRE-101, FG-PRE-102 and 18-150-0006) under IND 131464 to evaluate the safety and efficacy of 0.2% pilocarpine, 0.4% pilocarpine, 0.006% diclofenac and a combination of 0.2% pilocarpine with 0.006% diclofenac. Results from these studies showed that diclofenac did not significantly improve tolerability, safety or efficacy in subjects with presbyopia. Pilocarpine 0.4% demonstrated a higher efficacy than 0.2% pilocarpine. (b) (4)

The Phase 3 clinical development program in support of the proposed indication consists of 2 Phase 3 studies [Near 1 (20-150-0002) and Near 2 (20-150-0003)], which used the intended commercial formulation.

The following meetings were conducted under IND 131464 for this application:

- PIND Meeting 9/26/2016
- End of Phase 2 Meeting 3/9/2020
- Type C Meeting 8/25/2021
- Pre-NDA Meeting 8/17/2022

3.3. Foreign Regulatory Actions and Marketing History

Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4% is not approved in any foreign market.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI was consulted and inspected 2 sites (Drs. Debry and Restivo). Based on the results of these inspections, OSI found the data generated by these two clinical sites appear adequate. However, protocol deviations regarding study drug administration and data discrepancies were observed at Dr. Restivo's site. See the CDTL memorandum for additional detail.

4.2. Product Quality

CSF-1 ophthalmic solution is packaged in single-use transparent low-density polyethylene (LDPE) vials containing 0.4 mL solution.

The qualitative and quantitative composition of CSF-1 ophthalmic solution is presented below.

CSF-1 Ophthalmic Solution Composition

Component	Concentration		Quantity per unit[1] (mg)	Function	Quality Standard
	mg/mL	% w/v			
Pilocarpine hydrochloride	4.0	0.4	1.6	Drug substance	USP
Hypromellose (b) (4)	(b) (4)				USP-NF
Sodium chloride					USP-NF
Sodium hyaluronate					Ph. Eur.
Disodium edetate dihydrate					USP-NF
Sodium hydroxide	q.s. to target pH	q.s. to target pH	q.s. to target pH	pH adjuster	USP-NF
Hydrochloric acid					USP-NF
Water for Injection (WFI)	(b) (4)				USP-NF

USP: United States Pharmacopeia; mg: milligram; mL: milliliter; NF: National Formulary; Ph. Eur.: European Pharmacopeia; q.s: *quantum satis;* w/v: weight/volume

[1] Unit: is 0.4 mL ophthalmic solution per vial

Specifications for CSF-1 Ophthalmic Solution

Test Attributes	Analytical Procedure	Acceptance Criteria
General Attributes		
Appearance of Solution	Visual	Clear, colorless to slightly yellowish and slightly viscous solution, practically free of particles
Appearance of Immediate Packaging	Visual	A block of five transparent LDPE vials
Opalescence	Ph. Eur. 2.2.1	NMT reference suspension (b) (4)
pH	USP <791>	5.1 – 6.1
Osmolality	USP <785>	(b) (4) mOsm/Kg

Test Attributes	Analytical Procedure	Acceptance Criteria
Viscosity	USP <912>	(b) (4) cP
Minimum Fill	USP <755>	Mean volume (b) (4) 0.4 mL (b) (4) volume: ≥ (b) (4) mL
Particulate Matter	USP <789> Method 2	NMT 50 particles/mL ≥ (b) (4) µm NMT 5 particles/mL ≥ (b) (4) µm NMT 2 particles/mL ≥ (b) (4) µm
Leak Test[1]	Vacuum (b) (4)[2]	No leak[3]
Identification		
Identification of Pilocarpine HCl[1]	HPLC and UV (method 610)	1. The retention time of the main peak in sample chromatogram corresponds to that of the main peak in the standard preparation under the Assay determination conditions (RT ± 10%) 2. UV spectrum of the sample solution matches with that of the standard solution (UV maxima ±2 nm)
Assay		
Assay of Pilocarpine HCl (% of labeled amount)	HPLC (method 610)	(b) (4)
Assay of Disodium Edetate	HPLC (method 598)	(b) (4)
Degradation Products		
Degradation Products	HPLC (method 610)	Any individual unspecified degradation product: NMT (b) (4) %
		(b) (4)
Sterility		
Sterility	USP <71>	Complies

LDPE: Low-Density Polyethylene; NMT: Not More Than; USP: United States Pharmacopeia; Ph. Eur.: European Pharmacopoeia; HPLC: High-performance liquid chromatography

[1]Test performed at Release only

[2]Reference Section 3.2.P.3.5.8.1.1

[3]Results reported for IPC compliance. Any units detected with a leakage are automatically rejected.

4.3. Nonclinical Pharmacology/Toxicology

In embryofetal development studies, oral administration of pilocarpine to pregnant rats throughout organogenesis produced maternal toxicity, skeletal anomalies and reduction in fetal body weight at 90 mg/kg/day (approximately 1200-fold higher than the maximum recommended human ophthalmic dose [MRHOD] of 0.012mg/kg/day, on a mg/m^2 basis).

In peri-/postnatal study in rats, oral administration of pilocarpine during late gestation through lactation increased stillbirths at a dose of 36 mg/kg/day (approximately 475-fold higher than the MRHOD of 0.012mg/kg/day, on a mg/m^2 basis). Decrease neonatal survival and reduced mean body weight of pups were observed at ≥18mg/kg/day (approximately 240-fold higher than the MRHOD of 0.012mg/kg/day, on a mg/m^2 basis).

There are no data on the presence of pilocarpine in human milk, the effects on breastfed infants, or the effects on milk production to inform the risk of Qlosi to an infant during lactation. Systemic levels of pilocarpine following topical ocular administration are low ([see Clinical Pharmacology, (12.3)] , and it is not known whether measurable levels of pilocarpine would be present in maternal milk following ocular administration of Qlosi.

Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage level studies (up to 30 mg/kg/day; approximately 200-fold higher than the MRHOD of 0.012mg/kg/day, on a mg/m2 basis). In rats, an oral dose of 18 mg/kg/day (approximately 240-fold higher than the MRHOD of 0.012mg/kg/day, on a mg/m2 basis), resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both male and female rats, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats.

Pilocarpine did not show any potential to cause genetic toxicity in a series of studies that included: 1) bacterial assays (Salmonella and E. coli) for reverse gene mutations; 2) an in vitro chromosome aberration assay in a Chinese hamster ovary cell line; 3) an in vivo chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Fertility studies have not been conducted with Qlosi. Pilocarpine oral administration to male and female rats at a dosage of 18 mg/kg/day (approximately 240-fold higher than the MRHOD of 0.012mg/kg/day, on a mg/m^2 basis) resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphological evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on males, females, or both. In dogs, exposure to pilocarpine at a dosage of 3mg/kg/day for 6 months resulted in evidence of impaired spermatogenesis (approximately 135-fold higher than the MHROD of 0.012mg/kg/day, on a mg/m^2 basis).

4.4. Clinical Pharmacology

The Clinical Pharmacology review team has reviewed NDA 217836 and finds the application acceptable. PK of pilocarpine hydrochloride ophthalmic solution 0.4% was evaluated in healthy subjects (Study 21-100-0004). This study was open-label, 8-day multiple dose study in 15 healthy volunteers (HVs). Subjects were given CSF-1 ophthalmic solution in each eye twice a day (2 h apart) for 8 days. Following administration of two drops of CSF-1 ophthalmic solution in each eye daily (separated by 2 h) in healthy subjects for 8 days, plasma pilocarpine maximal

concentration of 766 (353.97) pg/mL was achieved at 2.25 h on Day 1, and 897 (287.24) pg/mL at 2.20 h on Day 8. The area under the concentration curve at time curve (AUC) were 2407 (1014.93) and 2991 (888.62) hr•pg/mL on Day 1 and Day 8, respectively. The accumulation ratio was 1.35 and 1.24 for Cmax and AUC, respectively.

Pilocarpine does not bind to human or rat plasma proteins over a concentration range of 5 to 25,000 ng/mL. The estimated $t_{1/2}$ of pilocarpine for Days 1 and 8 were 3.18 (0.90) and 3.96 (1.22) h, respectively.

4.5. Devices and Companion Diagnostic Issues

Based on the Genus decision, the Agency determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition.

In a January 3, 2023, email, the Office of Pharmaceutical Quality Application Team Lead confirmed that no CDRH Consult was needed for this application because the product is packaged in a single dose vial, and it is considered "low risk."

4.6. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name	Study Design	Test Product	Number of Subjects	Duration of Treatment
FG-PRE-101	Phase 2a, randomized, double masked, placebo controlled, repeat dose, crossover to support efficacy and safety	CSF-1-FDC (0.2% pilocarpine nitrate + 0.006% diclofenac sodium) or placebo	34 total CSF-1-FDC as first treatment: 15 Placebo as first treatment: 19	1 drop each morning to each eye for 2 weeks, 24-hour washout then opposite treatment for 2 weeks

Study Name	Study Design	Test Product	Number of Subjects	Duration of Treatment
FG-PRE-102	Phase 2a, randomized, double masked, placebo controlled, parallel arms, single dose to support efficacy and safety	CSF-1-FDC (24 subjects) or Placebo (12 subjects)	36	1 drop to each eye, single dose
18-150-0006	Phase 2b, randomized, double masked, parallel group, to support safety and efficacy	CSF-1-FDC	160	1 drop to each eye twice a day for 15 days
20-150-0002 (NEAR-1)	Phase 3, randomized, double masked, vehicle controlled to support efficacy and safety	CSF-1 (0.4% pilo HCL) (155 subjects) Vehicle control (154 subjects)	309	1 drop in each eye, repeated 2 hours later for one week, and 3 hours later for second week
20-150-0003 (NEAR-2)	Phase 3, randomized, double masked, vehicle controlled to support efficacy and safety	CSF-1 (0.4% pilo HCL) (154 subjects) Vehicle control (155 subjects)	304	1 drop in each eye, repeated 2 hours later for one week, and 3 hours later for second week
21-150-0005	Phase 3, randomized, double masked, vehicle controlled to support safety	CSF-1 (0.4% pilo HCL) (119 subjects) Vehicle control (59 subjects)	178	1 drop in each eye, repeated 2 to 3 hours later for 6 weeks

5.2. Review Strategy

The sources of clinical data utilized in this review include the studies listed in Section 5.1. The two studies which provide the main support for efficacy were: NEAR-1 (20-150-0002) and NEAR-2 (20-150-0003). The three studies which provide the main support for safety were: NEAR-1 (20-150-0002), NEAR-2 (20-150-0003) and Study 21-150-0005.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NEAR-1 (20-150-0002) and NEAR-2 (20-150-0003)

6.1.1. Study Design

NEAR-1 (20-150-0002): A Multicenter, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-1 Study: Near Eye-vision Acuity Restoration)

NEAR-2 (20-150-0003): A Multicenter, 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)

NEAR-1 and NEAR-2 were identically designed Phase 3, randomized, double-masked, Vehicle-controlled studies to examine the safety and efficacy of CSF-1. Their study design is presented here.

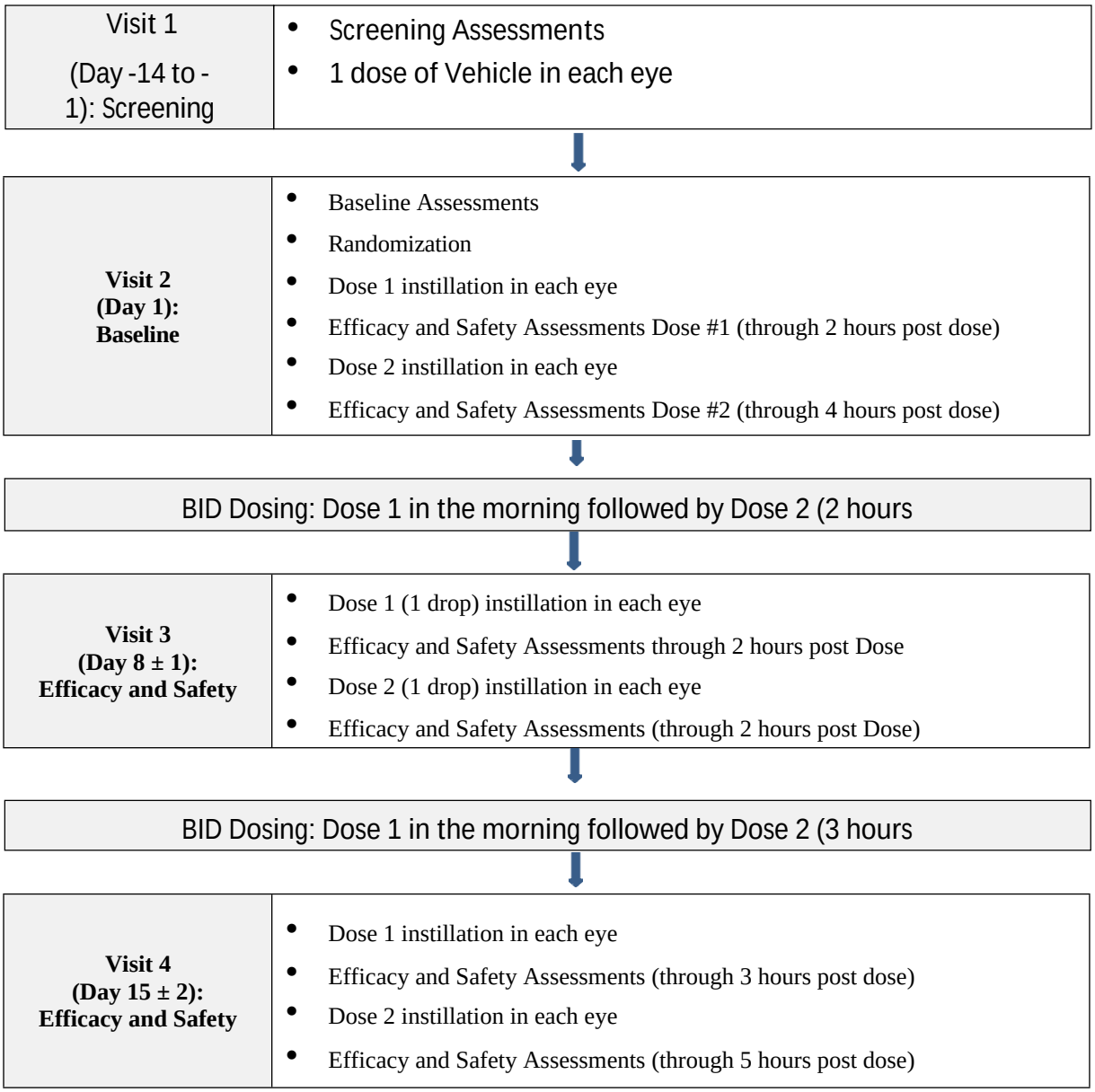
Overview and Objective

The objectives of this study were to evaluate the efficacy, safety and tolerability of CSF-1 [(pilocarpine hydrochloride ophthalmic solution) 0.4%] compared to vehicle when administered bilaterally, twice daily, in subjects with presbyopia.

Trial Design

This was a Phase 3 multicenter, randomized, double-masked, vehicle-controlled, parallel-group study evaluating the safety and efficacy of CSF-1 compared to Vehicle. Approximately 300 adult subjects ages 45 to 64 years with presbyopia were enrolled at approximately 18 clinical sites in the United States. Subjects who met all inclusion and exclusion criteria were randomized in a 1:1 ratio to receive one drop of either CSF-1 or vehicle bilaterally twice daily with approximately 2 hours between doses. Subjects were stratified by iris color (brown versus light [i.e., blue, green, gray, and hazel]) and baseline manifest refraction spherical equivalent (MRSE -0.5D, -0.5D to +0.75 D, and >+0.75). The study consisted of the following visits: Screening, Day 1, Day 8 and Day 15.

Schematic of the study design



Inclusion Criteria

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. Have Best Distance-Corrected Visual Acuity (BDCVA) at 40 cm $\geq$ 0.40 and $\leq$ 0.90 logarithm of the minimum angle of resolution (LogMAR, approximately between 20/50

and 20/160 Snellen) in at least 1 eye at Visit 1 prior to Vehicle dosing and in the same eye at Visit 2 (pre-treatment)
5. Have between -4.50 to +2.00 diopter (D) of sphere in each eye determined by manifest refraction (using negative cylinder for assessment of inclusion) and a $\leq$ 2.00 D difference between eyes at Visit 1
6. Have < 2.00 D of cylinder (using negative cylinder for assessment of inclusion) in each eye determined by manifest refraction at Visit 1
7. Have a $\leq$ 0.04 LogMAR (i.e., approximately 20/20-2 Snellen or better) BDCVA at 4 m in each eye at Visit 1 prior to Vehicle dosing
8. Have a negative urine pregnancy test at Visit 1, if female of childbearing potential (those who have experienced menarche and who were 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

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, whether active or inactive
5. Have a known history or diagnosis of ocular herpetic infection, iritis, scleritis, or uveitis in either eye, whether active or inactive
6. Have undergone or plan to have any form of refractive eye surgery within the study period, including incisional keratotomy, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), laser-assisted sub-epithelial keratectomy (LASEK), corneal inlay procedures, conductive keratoplasty, small incision lenticule extraction, cataract extraction, or any form of intraocular lens implantation
7. Be unable to or refuse to discontinue soft contact lens wear 7 days prior to study Visit 1 and rigid gas permeable 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 (Ora

CalibraTM 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. Have a > 0.14 LogMAR (i.e., 7 letters) improvement in post-Vehicle treatment (at 15 minutes post-Vehicle treatment) monocular BDCVA in either eye at 40 cm compared to Visit 1 pre-treatment, or a > 0.14 LogMAR (i.e., 7 letters) improvement in monocular BDCVA in either eye at 40 cm between Visit 1 (pre-treatment) and Visit 2 (pre-treatment baseline)
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 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 1or planned surgical intervention within 30 days after Visit 4
17. Use any of the following prohibited systemic medications during the indicated timeframe:
    a. Day of 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®).
    b. 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 8 & above])
- any other medication affecting the pupil or accommodation
- 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

Treatments Administered

The study interventions used in this study were CSF-1 or its vehicle, dosed at 1 drop in each eye twice a day, 2 to 3 hours apart. The first daily dose occurred in the morning, with the second dose 2 hours later (+1 hour) for approximately 1 week. Following Visit 3 (Day 8), the first daily dose occurred in the morning with the second dose 3 hours later (+1 hour). Subjects were instructed not to dose at home on clinic visit days.

Study Flow Chart

Study Parameter	Visit 1 (Day -14 to -1)	Visit 2 (Day 1)	Visit 3 (Day 8 ± 1)	Visit 4 (Day 15 ± 2)
Informed consent / HIPAA	X			
Demographic data	X			
Medical and medication history	X			
Medical and medication history update		X	X	X
Urine pregnancy test (for females of childbearing potential)	X			X
Inclusion and exclusion criteria review	X	X		
Manifest refraction	X			
Dark-adapted pupillometry	X			
Pre-treatment pupillometry under near visual acuity at 40 cm testing conditions	X	X	X	X
Pre-treatment monocular near BDCVA 40 cm (Precision Vision Chart) [a]	X	X	X	X
Pre-treatment binocular near BDCVA at 40 cm (Precision Vision Chart) [a]	X	X	X	X
Pre-treatment monocular BDCVA at 4 m (ETDRS)[a]	X	X	X	X
Pre-treatment monocular low-luminance BDCVA at 4 m (ETDRS) [a]	X	X	X	X
Pre-treatment slit-lamp biomicroscopy	X	X	X	X
Pre-treatment conjunctival redness assessment [b]	X	X	X	X
Instillation of Vehicle OU	X			
Vehicle post-treatment monocular near BDCVA at 40 cm (Precision Vision Chart) (15 minutes post-vehicle) [a]	X			
Adverse event query [c]	X			
Selection of study eye		X		

Study Parameter	Visit 1 (Day -14 to -1)	Visit 2 (Day 1)	Visit 3 (Day 8 ± 1)	Visit 4 (Day 15 ± 2)
Randomization		X		
Instillation of Dose 1 study drug		X	X	X
Study drug drop comfort assessment immediately upon instillation, 30 seconds, and 1, 5, and 10 minutes post Dose 1[d]		X	X	X
Post-Dose 1 pupillometry under near visual acuity at 40 cm testing conditions (30 minutes and 1 and 2 hours post-treatment)[a,c]		X		
Post-Dose 1 monocular near BDCVA at 40 cm (Precision Vision Chart) (30 minutes and 1, and 2 hours post-treatment) [a,c]		X		
Post-Dose 1 binocular near BDCVA at 40 cm (30 minutes and 1 and 2 hours post-treatment) [a,c]		X		
Post-Dose 1 monocular BDCVA at 4 m (30 minutes and 1 and 2 hours post-treatment) [a,c]		X		
Post-Dose 1 monocular LL-BDCVA at 4 m 1 hour post- treatment [a,c]		X	X	X
Post-Dose 1 pupillometry under near visual acuity at 40 cm testing conditions (1 and 2 hours post-treatment) [a,c]			X	
Post-Dose 1 monocular near BDCVA at 40 cm (Precision Vision Chart) (1 and 2 hours post-treatment) [a,c]			X	
Post-Dose 1 binocular near BDCVA at 40 cm (Precision Vision Chart) (1 and 2 hours post-treatment) [a,c]			X	
Post-Dose 1 monocular BDCVA at 4 m (1 and 2 hours post- treatment) [a,c]			X	
Post-Dose 1 pupillometry under near visual acuity at 40 cm testing conditions (Precision Vision Chart) (20 minutes, 1, 2, and 3 hours post- treatment) [a,c]				X
Post-Dose 1 monocular near BDCVA at 40 cm (Precision Vision Chart) (20 minutes, 1, 2, and 3 hours post-treatment) [a,c]				X
Post-Dose 1 binocular near BDCVA at 40 cm (Precision Vision Chart) (20 minutes, 1, 2, and 3 hours post-treatment) [a,c]				X
Post Dose 1 monocular BDCVA at 4 m (Precision Vision Chart) (20 minutes, 1, 2, and 3 hours post-treatment) [a,c]				X
Post-Dose 1 conjunctival redness assessment [b,c]		X	X	X
Instillation of Dose 2 study drug		X	X	X
Post-Dose 2 pupillometry under near visual acuity at 40 cm testing conditions (30 minutes and 1,2, 3, and 4 hours post-treatment) [a,c]		X		
Post-Dose 2 monocular near BDCVA at 40 cm (Precision Vision Chart) (30 minutes, 1, 2, 3, and 4 hours post-treatment) [a,c]		X		
Post-Dose 2 binocular near BDCVA at 40 cm (Precision Vision Chart) (30 minutes, 1, 2, 3, and 4 hours post-treatment) [a,c]		X		
Post-Dose 2 monocular BDCVA at 4 m (30 minutes, 1, 2, 3, and 4 hours post-treatment) [a,c]		X		
Post-Dose 2 pupillometry under near visual acuity at 40 cm testing conditions (1 and 2 hours post-treatment) [a,c]			X	
Post-Dose 2 monocular near BDCVA at 40 cm (Precision Vision Chart) (1 and 2 hours post-treatment) [a,c]			X	
Post-Dose 2 binocular near BDCVA at 40 cm (Precision Vision Chart) (1 and 2 hours post-treatment) [a,c]			X	
Post-Dose 2 monocular BDCVA at 4 m (1 and 2 hours post- treatment) [a,c]			X	

Study Parameter	Visit 1 (Day -14 to -1)	Visit 2 (Day 1)	Visit 3 (Day 8 ± 1)	Visit 4 (Day 15 ± 2)
Post-Dose 2 monocular LL-BDCVA at 4 m 1 hour post- treatment [a,c]		X	X	X
Post-Dose 2 pupillometry under near visual acuity at 40 cm testing conditions (20 minutes, 1, 2, 3, 4, and 5 hours post-treatment) [a,c]				X
Post-Dose 2 monocular near BDCVA at 40 cm (Precision Vision Chart) (20 minutes, 1, 2, 3, 4, and 5 hours post-treatment) [a,c]				X
Post-Dose 2 binocular near BDCVA at 40 cm (Precision Vision Chart) (20 minutes, 1, 2, 3, 4, and 5 hours post-treatment) [a,c]				X
Post-Dose 2 monocular BDCVA at 4 m (20 minutes, 1, 2, 3, 4, and 5 hours post-treatment) [a,c]				X
AE query (post-treatment) [c]		X	X	X
End of visit conjunctival redness assessment		X	X	X
End of visit slit-lamp biomicroscopy	X	X	X	X
Fluorescein staining	X			
IOP	X	X	X	X
Dilated indirect ophthalmoscopy	X			X
Dispense study drug / dosing diary		X	X	
Collect study drug / dosing diary			X	X
Study exit				X

Abbreviations: AE = adverse event; BDCVA = best distance-corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study;
HIPAA = Health Information Portability and Accountability Act; IOP = intraocular pressure; LL-BDCVA= low-luminance best distance-corrected visual acuity; OU = both eyes

[a] Visual acuity was assessed with best distance-correction determined by the manifest refraction at Visit 1.

[b] Conjunctival redness was assessed using an Ora Calibra 0–4 picture grading scale. Post Dose 1 assessments was conducted at the 20 minutes and 1 hour time point.

[c] Minimum/maximum windows are defined below for any post-vehicle/post-treatment assessment time point:

- 15 minute time point - ± 5 minutes
- 20 minute time point - ± 5 minutes
- 30 minute time point - ± 5 minutes
- 1 hour time point - ± 10 minutes
- 2 hour time point - ± 10 minutes
- 3 hour time point - ± 10 minutes
- 4 hour time point - ± 10 minutes
- 5 hour time point - ± 10 minutes

[d] Study drug drop comfort assessment was performed immediately, 30 seconds, and 1, 5, and 10 minutes post Dose 1 using a 0–10 Drop Comfort scale Note: Pre-treatment indicates that an assessment was performed prior to any treatment during that study visit.

NEAR-1 List of Investigators

Site Number	Principal Investigator Name and Address	Number of Subjects Randomized
10	Evans, David G. Total Eye Care, PA, 6060 Primacy Parkway, Suite 200. Memphis, TN 38119	70
11	Christie, William C. Scott & Christie and Associates 105 Brandt Drive, Suites 201, 202, 204 Cranberry Township, PA 16066	10
13	Charles, Keith C. Mid-Florida Eye Center, 17560 Hwy. 441 Mount Dora, FL 32757	16
14	Kim, Jennifer Lee Clayton Eye Center, 1000 Corporate Center Drive, Suite 100,120,180,240 Morrow, Ga 30260	3
15	Alpern, Louis M. The Cataract & Glaucoma Center 4171 N. Mesa Bldg D, Suite 100 El Paso, Tx 79902	21
16	Gira, Joseph P. Ophthalmology Consultants, Ltd 12692 Lamplighter Square St. Louis Missouri 63128	1
17	El-Harazi, Sherif Mustafa Global Research Management 1510 S. Central Avenue, Suite 300 Glendale, CA 91204	44
18	Swarup, Jitendra Albemarle Eye Center, PLLC 1503 North Road Street Elizabeth City, NC 27909	20
19	Silverstein, Steven M. Silverstein Eye Centers, 4240 Blue Ridge Blvd. Suite 1000 Kansas City, Missouri 64133	8
20	Walman, Gerald B. Arizona Eye Center, 1500 W. Ray Road Chandler, AZ 85224	26
21	DeBry, Peter W. NV Eye Surgery, 2390 W. Horizon Ridge Pkwy. Henderson NV 89052	46
22	Bucci, Frank A., Jr. Bucci Laser Vision, 158 Wilkes-Barre Township Blvd Wilkes-Barre, PA 18702	0
24	Stahl, Jason E. Durrie Vision 8300 College Blvd	14
25	Khachikian, Stephen	9

	Black Hills Regional Eye Institute 2800 Third Street Rapid City SD 57701	
26	Meyer, John C. The Eye Care Institute, 1536 Story Avenue Louisville, KY 40206	5
27	Smith, Stephen E. Eye Associates of Fort Myers, 4225 Evans Ave Fort Myers, FL 33901	4
29	Liu, Alex C East West Eye Institute/Premiere Practice Management, LLC, 420 E. 3rd St. Suite 603 Los Angeles CA 90013	12

NEAR -2 List of Investigators

Site Number	Principal Investigator Name and Address	Number of Subjects Randomized
30	Wirta, David L. Eye Research Foundation, 520 Superior Ave #235 Newport Beach, CA 92663	40
31	Moshirfar, Majid Hoopes Vision Hoopes, Durrie Rivera Research 11820 S. State Street, Suite 200 Draper, UT 84020	17
33	Segal, Bruce A. Glaucoma Specialists of South Florida 5258 Linton Blvd #302 Delray Beach, FL 33484	10
34	Hartman, Paul J. Rochester Ophthalmological Group, PC 2100 S. Clinton Avenue Rochester, NY 14618	29
35	Depenbusch, Michael J. Arizona Eye Center, 1500 W. Ray Rd. Chandler, AZ 85225	17
37	Reiser, Harvey J. Eye Care Specialists, 703 Rutter Avenue Kingston, PA 18704	14
38	Smyth-Medina, Robert J. North Valley Eye Medical Group, Inc. 11550 Indian Hills Rd. #341 Mission Hills, CA 91345	25
40	Paauw, James D. Piedmont Eye Center, 116 Nationwide Drive Lynchburg VA, 24502	1
41	Restivo, Vincent A. Hill Country Eye Center	29

	11901 West Parmer Lane #400 Cedar Park, TX 78613	
42	Liu, Norman H. Orange County Ophthalmology Medical Group 12665 Garden Grove Blvd. #401 Garden Grove, CA 92843	6
43	Reilly, Charles D. R and R Eye Research, LLC 5430 Fredericksburg Rd, #100 San Antonio, TX 78229	23
44	Heller, Matthew A. Eye Doctors of Arizona, 3321 E Bell Road #B-12 Phoenix, AZ 85032	29
45	Peterson, Jared D. Alpine Research Organization 1407 N 2000 W #A Clinton, UT 84015	2
46	Paul, Matthew D. Danbury Eye Physicians, 69 Sand Pit Road Danbury, CT 06810	15
48	Borisuth, Navaneet S. Virdi Eye Clinic, 4600 30th Street Rock Island, IL 61201	8
50	Hammond, Matthew D. *Herion, Michael A., Carrot Eye Center 1500 S Dobson Rd. #313 Mesa, AZ 85202	19
51	Bacharach, Jason North Bay Eye Associates, 104 Lynch Creek Way #15 Petaluma, CA 94954	10
52	Forstot, S. Lance Colorado Eye Consultants/ Corneal Consultants of Colorado PC, 1501 W. Mineral Ave. Littleton, CO 80120	10

Study Endpoints

Primary Efficacy Endpoint

- 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 at Visit 3 (Day 8), 1 hour following Dose 1

Key Secondary Efficacy Endpoint

- 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 at:

  - Visit 3 (Day 8), 2 hours following Dose 1
  - Visit 3 (Day 8), 1 hour following Dose 2
  - Visit 3 (Day 8), 2 hours following Dose 2

Secondary Efficacy Endpoints

- The percentage of subjects with a response; response was defined as 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 at the following visits, doses, and time points:
  - Visit 2 (Day 1), 30 minutes following Dose 1
  - Visit 2 (Day 1), 1 hour following Dose 1
  - Visit 2 (Day 1), 2 hours following Dose 1
  - Visit 2 (Day 1), 30 minutes following Dose 2
  - Visit 2 (Day 1), 1 hour following Dose 2
  - Visit 2 (Day 1), 2 hours following Dose 2
  - Visit 2 (Day 1), 3 hours following Dose 2, sustained
  - Visit 2 (Day 1), 4 hours following Dose 2, sustained
  - Visit 4 (Day 15), 20 minutes following Dose 1
  - Visit 4 (Day 15), 1 hour following Dose 1
  - Visit 4 (Day 15), 2 hours following Dose 1
  - Visit 4 (Day 15), 3 hours following Dose 1, sustained
  - Visit 4 (Day 15), 20 minutes following Dose 2
  - Visit 4 (Day 15), 1 hour following Dose 2
  - Visit 4 (Day 15), 2 hours following Dose 2
  - Visit 4 (Day 15), 3 hours following Dose 2, sustained
  - Visit 4 (Day 15), 4 hours following Dose 2, sustained
  - Visit 4 (Day 15), 5 hours following Dose 2, sustained

Time points termed “sustained” required the subject to have a response at the indicated time point as well as all earlier time points, back to 1 hour within the same dose and visit.

Exploratory Efficacy Endpoints

- Subjects with a ≥ 2-line (10-letter) gain from baseline in near visual acuity, with or without the “sustained” requirement, as well as with and without the requirement of no loss of ≥ 1-line (5-letter) from baseline in distance visual acuity.
  - Percentage of subjects with a ≥ 2-line (10-letter) gain from baseline in BDCVA at 40 cm (Precision Vision Chart) and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) at each time point [for each time point value and sustained time point values] at Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15) in the study eye following Dose 1 and Dose 2.
  - Percentage of subjects with a sustained ≥ 2-line (10-letter) gain from baseline in

BDCVA (Precision Vision chart at 40 cm) in the study eye at each time point and visit
    - Percentage of subjects with a ≥ 2-line (10-letter) gain from baseline in BDCVA (Precision Vision chart at 40 cm) in the study eye at each time point and Visit (with no sustained criteria requirement at any time point).
- Subjects with a ≥ 3-line (15-letter) gain from baseline in near visual acuity, with or without the "sustained" requirement, as well as with and without the requirement of no loss of ≥ 1-line (5-letter) from baseline in distance visual acuity.
    - 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) at each time point at Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15) in the study eye following Dose 1 and Dose 2 without the requirement for sustained response. This analysis is referred to as "standard" analysis for this clinical study report (CSR), as most clinical studies in subjects with presbyopia measure 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) without reference to a sustained criterion.
    - Percentage of subjects with a sustained ≥ 3-line (15-letter) gain from baseline in BDCVA (Precision Vision chart at 40 cm) in the study eye at each time point and visit. This analysis assessed the effect with the requirement of a sustained response at all time points starting from 2 hours post dose throughout the last dose.
    - Percentage of subjects with a ≥ 3-line (15-letter) gain from baseline in BDCVA (Precision Vision chart at 40 cm) in the study eye at each time point and Visit (with no sustained criteria requirement at any time point).
- Change from baseline in pupil diameter under near VA testing conditions.
    - Mean change in pupil diameter under near VA at 40 cm testing conditions, from baseline at each time point at Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15) in the study eye.

Statistical Analysis Plan

Study Populations

- Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of the study drug. Subjects in the FAS were analyzed as randomized. The FAS was used as the primary analysis set for the determination of efficacy.
- Per Protocol Set (PPS) included subjects in the FAS who did not have a major protocol deviation. Protocol deviations were assessed prior to database lock and unmasking. Subjects in the PPS were analyzed as treated. The PPS were supportive of the primary and key secondary efficacy analysis performed with FAS.
- Safety Set (SAF) included all subjects who received at least 1 dose of study drug.

Subjects in the SAF were analyzed as treated.

Primary Efficacy Analysis

The primary endpoint efficacy analyses were conducted in the FAS with missing data handled as follows:

- Discontinuation of study drug and non-optimal compliance was ignored.
- Withdrawal due to lack of efficacy or AEs: missing data was singly imputed as failure.
- Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs: missing data were imputed employing MI using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology.

No subject data were excluded from the FAS due to protocol violations/deviations. Multiple imputations of missing values were completed for the continuous measures (BDCVA at 40 cm and BDCVA at 4 m), therefrom the response variable was determined. Imputation of failure due to lack of efficacy or AE was assigned after multiple imputation (MI) was performed.

Variables for treatment group, baseline for BDCVA at 40 cm, and baseline for BDCVA at 4 m were also included in the multiple imputation model. Twenty-five complete imputed datasets were created.

For each imputed dataset, a logistic regression model with baseline BDCVA at 40 cm as a covariate and treatment as a main effect was used to obtain the treatment effect estimate, odds ratio, and 95% confidence interval (CI) for odds ratio.

6.1.2. Study Results

Compliance with Good Clinical Practices

NEAR-1 (020-150-0002) and NEAR-2 (020-150-0003)

These studies were conducted in compliance with GCP and is registered at clinicaltrials.gov, registration # NCT04599933 and # NCT04599972, respectively.

Analysis Populations

NEAR-1(020-150-0002): Analysis Populations

	CSF-1	Vehicle
Full Analysis Set (FAS)	155	154
Per Protocol Set (PPS)	149	144
Safety Set (SAF)	155	154

NEAR-2(020-150-0003): Analysis Populations

	CSF-1	Vehicle
Full Analysis Set (FAS)	154	150
Per Protocol Set (PPS)	147	145
Safety Set (SAF)	153	151

Reviewer's comment: *The Full Analysis Set was defined as all randomized subjects who received at least 1 dose of the study drug and was used for the primary efficacy analysis.*

Patient Disposition

NEAR-1(020-150-0002): Patient Disposition

	CSF-1 N=155	Vehicle N=154
Number of Patients Randomized	155	154
Number of Patients Treated	155	154
Number of Patients Completed Study	146	147
Number of Patients Discontinued From Study	9	7
Reasons for Discontinuation		
Adverse Event	4	1
Lack of Efficacy	0	0
Screen Failure	1	2
Withdrawal by Subject	4	2
Lost to F/U	0	1
Physician Decision	0	1

NEAR-2(020-150-0003): Patient Disposition

	CSF-1 N=154[a]	Vehicle N=150
Number of Patients Randomized	154	150
Number of Patients Treated	154	150
Number of Patients Completed Study	144	142
Number of Patients Discontinued From Study	10	8

Reasons for Discontinuation		
Adverse Event	2	1
Lack of Efficacy	0	0
Protocol Violation	1	0
Withdrawal by Subject	6	1
Lost to F/U	1	6
Other	1	0

[a] One subject was randomized to CSF-1 and inadvertently received Vehicle.

Protocol Violations/Deviations

NEAR-1(020-150-0002): Protocol Deviations

	CSF-1 N=155	Vehicle N=154
Overall	6	10
Inclusion/exclusion and randomization	4	7
Visit out of window	2	2
Subject's failure to follow instructions	0	1

Reviewer's Comment:
A total of 16 participants (5.2%) had protocol deviations during the study (6/155 [3.9%] in the CSF-1 group and 10/154 [6.5%] in the vehicle group). In the CSF-1 group, the significant deviations were due to inclusion/exclusion criteria and a visit out of the window. In the vehicle group, the significant deviations were due to inclusion criteria, a visit out of the window, and a subject's failure to follow instructions in the subject diary.

NEAR-2(020-150-0003): Protocol Deviations

	CSF-1 N=154	Vehicle N=150
Overall	7	5
Inclusion/exclusion and randomization	4	3
Visit out of window	1	2
Subject's noncompliance with test article/study drug	1	0
Improper protocol procedures at site	1	0

Reviewer's Comment:
A total of 12 participants (3.9%) had protocol deviations during the study (7/154 [4.5%] in the CSF-1 group and 5/150 [3.3%] in the vehicle group). In the CSF-1 group, the significant deviations were due to inclusion/exclusion criteria. One subject had a visit out of the window, 1 subject left the study drug in the car outside of temperature range and used the vials incorrectly

and 1 subject was given vehicle instead of CSF-1 per randomization. In the vehicle group, the significant deviations were due to inclusion criteria and visits out of the window.

Table of Demographic Characteristics

APPEARS THIS WAY ON ORIGINAL

Demographics

	NEAR-1(020-150-0002)		NEAR-2(020-150-0003)	
	CSF-1 N=155	Vehicle N=154	CSF-1 N=154	Vehicle N=150
Age				
Mean (SD)	54.8 (4.56)	54.5 (4.88)	54.6 (4.97)	54.8 (4.81)
Min, Max	45, 64	45, 64	45, 64	45, 64
Sex				
Male (%)	62 (40.0)	62 (40.3)	53 (34.4)	56 (37.3)
Female (%)	93 (60.0)	92 (59.7)	101 (65.6)	94 (62.7)
Race				
White (%)	121 (78.1)	111 (72.1)	131 (85.1)	132 (88.0)
African American (%)	25 (16.1)	25 (16.2)	13 (8.4)	9 (6.0)
Asian (%)	6 (3.9)	14 (9.1)	5 (3.2)	7 (4.7)
American Indian (%)	2 (1.3)	2 (1.3)	0	1 (0.7)
Multi-Racial (%)	0	1 (0.6)	3 (1.9)	0
Other (%)	1 (0.6)	1 (0.6)	0	1 (0.7)
Ethnicity				
Hispanic or Latino	33 (21.3)	23 (14.9)	30 (19.5)	28 (18.7)
Not Hispanic or Latino	122 (78.7)	131 (85.1)	124 (80.5)	122 (81.3)

Reviewer's Comment: *Baseline demographics were balanced between treatment groups for both studies.*

Baseline Ocular Characteristics

Baseline Characteristics

	NEAR-1(020-150-0002):		NEAR-2(020-150-0003)	
	CSF-1 N=155	Vehicle N=154	CSF-1 N=154	Vehicle N=150
Iris Color: n (%)				
Dark	84 (54.2)	84 (54.5)	72 (46.8)	70 (46.7)
Light	71 (45.8)	70 (45.5)	82 (53.2)	80 (53.3)
Iris Color: n (%)				
Blue	32 (20.6)	39 (25.3)	34 (22.1)	49 (32.7)
Brown	83 (53.5)	85 (55.2)	71 (46.1)	70 (46.7)
Hazel	29 (18.7)	19 (12.3)	34 (22.1)	17 (11.3)
Green	9 (5.8)	11 (7.1)	13 (8.4)	11 (7.1)
Gray	2 (1.3)	0	2 (1.3)	3 (2.0)
Manifest Refraction Spherical Equivalent: n (%)				
-4.5 D to < -0.5 D	35 (22.6)	32 (20.8)	31 (20.1)	30 (20.0)
-0.5 D to ≤ +0.75 D	88 (56.8)	90 (58.4)	91 (59.1)	89 (59.3)
> +0.75 D to +2.0 D	32 (20.6)	32 (20.8)	72 (46.8)	70 (46.7)

Reviewer's Comment: *The randomization was stratified for iris color and manifest refraction spherical equivalent. Baseline ocular characteristics were balanced between treatment groups for both studies.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance and concomitant medications were recorded for all subjects and were balanced between treatment groups.

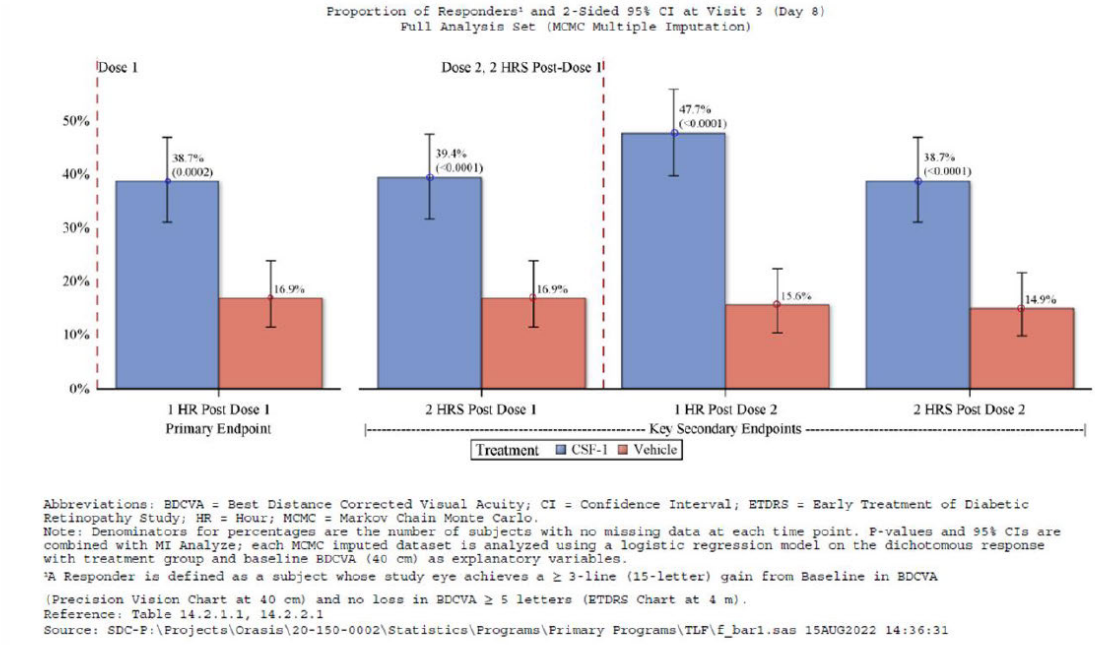
Efficacy Results – Primary Endpoint

NEAR-1(020-150-0002)
Missing data due to withdrawal from lack of efficacy was imputed as failure. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs were imputed employing multiple imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology. For each imputed dataset, a logistic regression model with baseline BDCVA at 40 cm as a covariate and treatment as a main effect was used to obtain the treatment effect estimate, odds ratio, and 95% confidence interval (CI) for odds ratio.

NEAR-1(020-150-0002): Analysis of Subjects with 3-Line Improvement of BDCVA at 40 cm and no loss of ≥ 5 letters of BDCVA at 4m at Visit 3 (Day 8), 1 hour post Dose 1 (FAS population)

	CSF-1 N=155	Vehicle N=154
Day 8, 1 Hour Post-Dose 1		
Number (%) of Responders	60 (38.7)	26 (16.9)
Number (%) of Non-Responders	95 (61.3)	128 (83.1)
Treatment Comparisons		
Odds Ratio	2.916	
95% CI of Odds Ration	(1.663, 5.113)	
p-value	0.0002	

Visit 3 (Day 8): Primary and Key Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS MCMC Multiple Imputation)



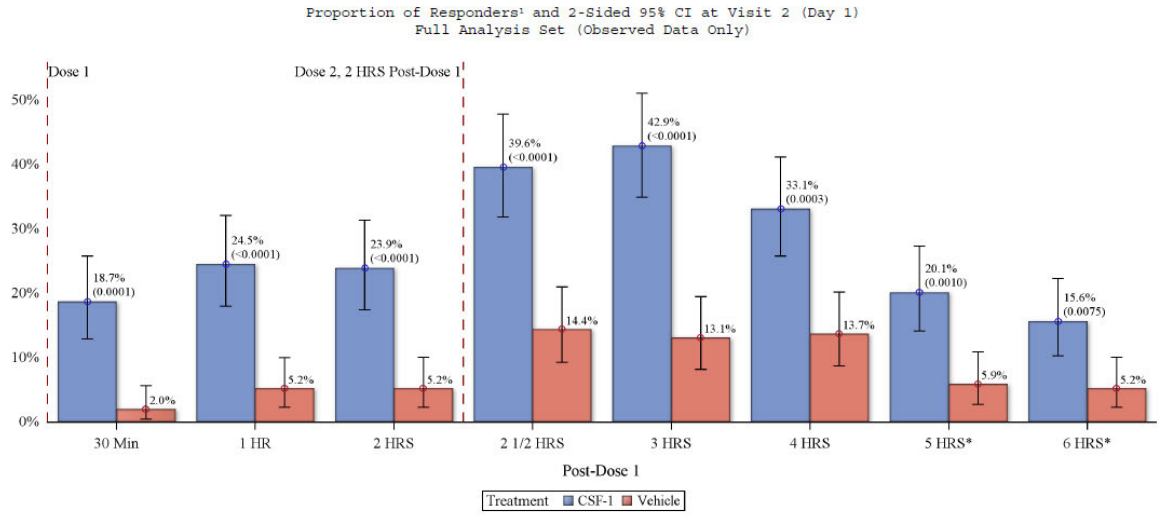
Abbreviations: BDCVA = Best Distance Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment of Diabetic Retinopathy Study; HR = Hour; MCMC = Markov Chain Monte Carlo.
Note: Denominators for percentages are the number of subjects with no missing data at each time point. P-values and 95% CIs are combined with MI Analyze; each MCMC imputed dataset is analyzed using a logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables.
[1]A Responder is defined as a subject whose study eye achieves a ≥ 3-line (15-letter) gain from Baseline in BDCVA
(Precision Vision Chart at 40 cm) and no loss in BDCVA ≥ 5 letters (ETDRS Chart at 4 m).
Reference: Table 14.2.1.1, 14.2.2.1
Source: SDC-P:\Projects\Orasis\20-150-0002\Statistics\Programs\Primary Programs\TLF\f_bar1.sas 15AUG2022 14:36:31

Sources: Tables 14.2.1.1 and 14.2.2.1

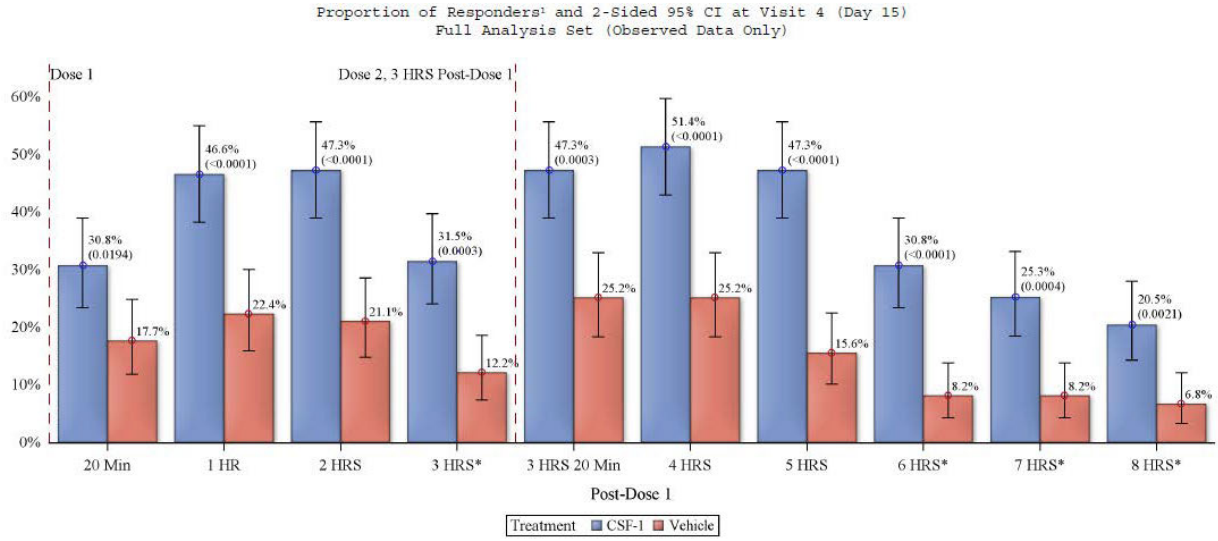
Reviewer's Comment:

In NEAR-1(020-150-0002), at Visit 3 (Day 8) 1 hour post Dose 1, a statistically significant greater percentage of subjects had improvement of ≥ 3-lines (15-letters) in monocular BDCVA at 40 cm and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) in the CSF-1 group (n = 60; 38.7%; p = 0.0002) compared to the Vehicle group (n = 26; 16.9%).

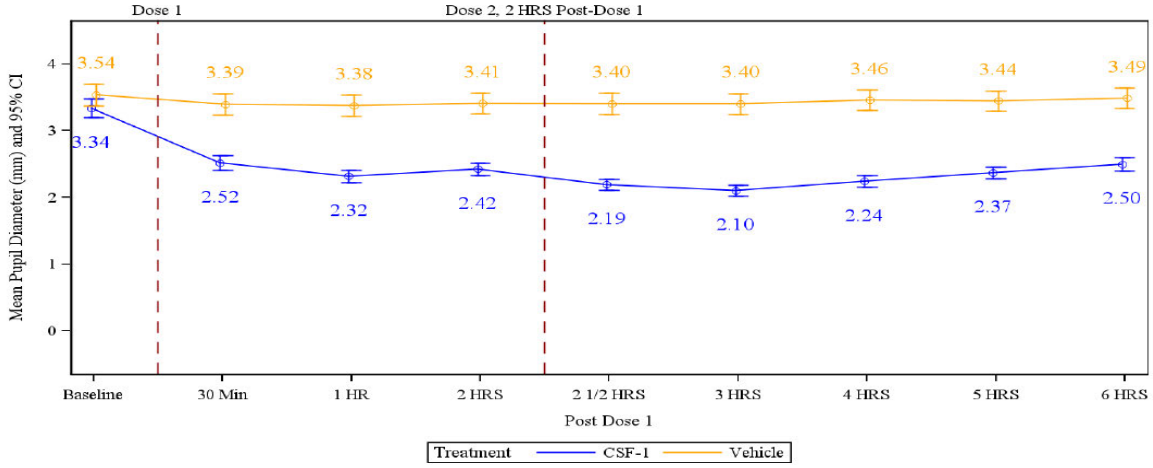
Visit 2 (Day 1): Other Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) at (FAS Observed Data Only)



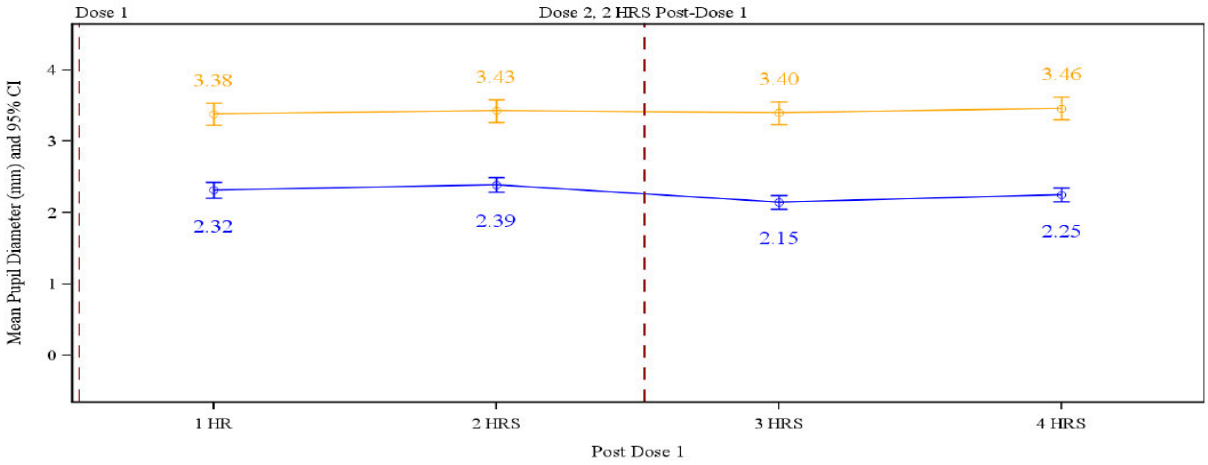
Visit 4 (Day 15): Other Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS Observed Data Only)



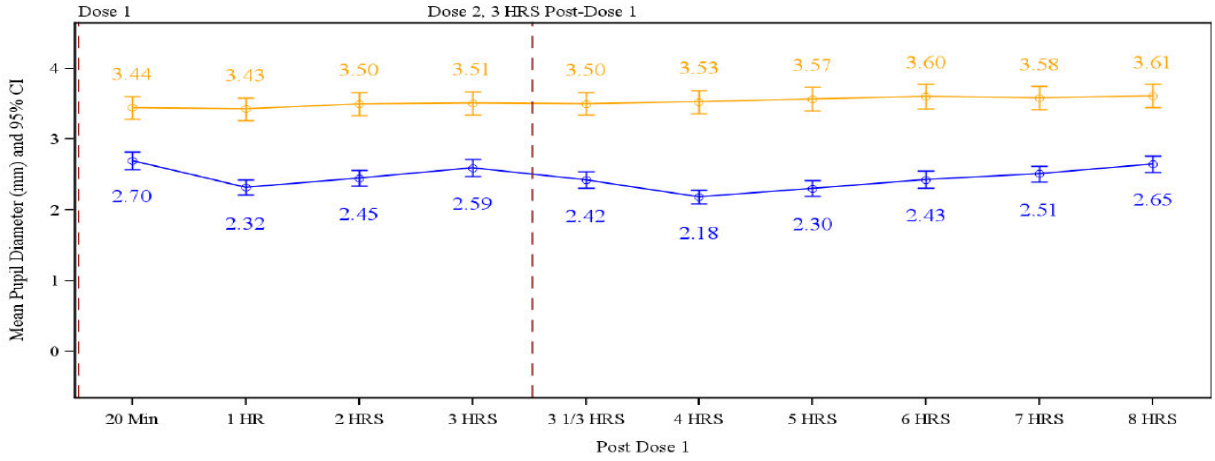
Visit 2 (Day 1): Mean Pupil Diameter Under Near VA at 40 cm



Visit 3 (Day 8): Mean Pupil Diameter Under Near VA at 40 cm



Visit 4 (Day 15): Mean Pupil Diameter Under Near VA at 40 cm



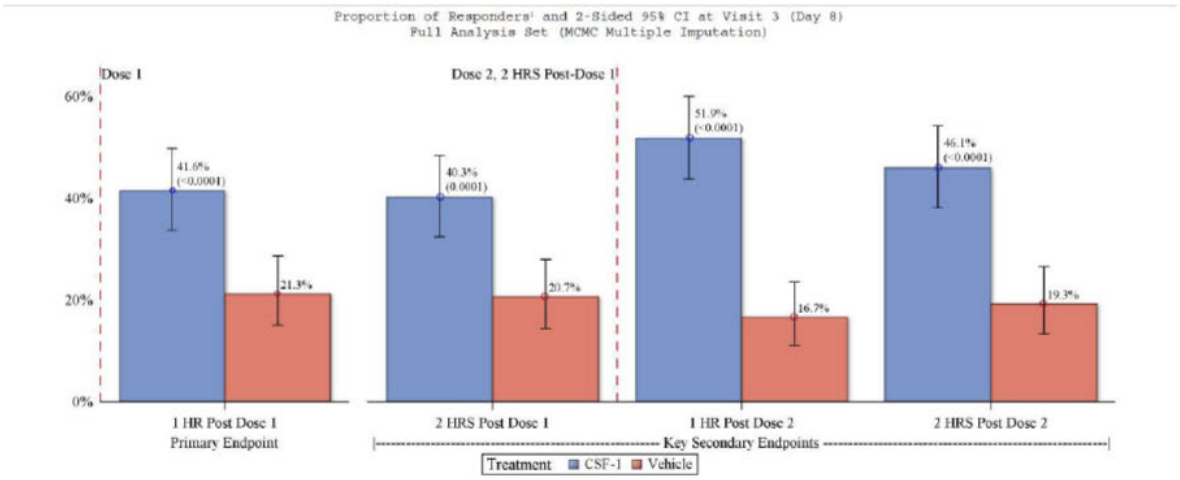
NEAR-2 (020-150-0003)
Missing data due to withdrawal from lack of efficacy was imputed as failure. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs were imputed employing MI using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology. For each imputed dataset, a logistic regression model with baseline BDCVA at 40 cm as a covariate and treatment as a main effect was used to obtain the treatment effect estimate, odds ratio, and 95% confidence interval (CI) for odds ratio.

NEAR-2 (020-150-0003): Analysis of Subjects with 3-Line Improvement of BDCVA at 40 cm and no loss of $\geq$ 5 letters of BDCVA at 4m at Visit 3 (Day 8), 1 hour post Dose 1 (FAS population)

	Including site #41		Excluding site #41	
	CSF-1 N=154	Vehicle N=150	CSF-1 N=138	Vehicle N=137
Day 8, 1 Hour Post-Dose 1				
Number (%) of Responders	64 (41.6)	32 (21.3)	56 (40.6)	30 (21.9)
Number (%) of Non-Responders	90 (58.4)	118 (78.7)	82 (59.4)	107 (78.1)
Treatment Comparisons				
Odds Ratio	2.979		2.708	
95% CI of Odds Ration	(1.753, 5.064)		(1.560, 4.699)	
p-value	<0.0001		0.0004	

Reviewer's Comment:
See the CDTL memorandum. Based on the results of clinical site inspections, protocol deviations regarding study drug administration and data discrepancies were observed at site #41. As per an IR sent to the Applicant on August 10, 2023, the Applicant submitted an analysis of the primary efficacy endpoint with site #41 excluded. The results are not significantly altered.

Visit 3 (Day 8): Primary and Key Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS MCMC Multiple Imputation)



Sources: Tables 14.2.1.1 and 14.2.2.1

Reviewer's Comment:

In NEAR-2 (020-150-0003), at Visit 3 (Day 8) 1 hour post Dose 1, a statistically significant greater percentage of subjects had improvement of ≥ 3-lines (15-letters) in monocular BDCVA at 40 cm and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) in the CSF-1 group ([n = 64; 41.6%; p <0.0001,including site #41] and [n=56; 40.6%; p=0.004, excluding site #41]) compared to the Vehicle group ([n = 32; 21.3%, including site #41] and [n=30; 21.9%, excluding site #41])

Data Quality and Integrity

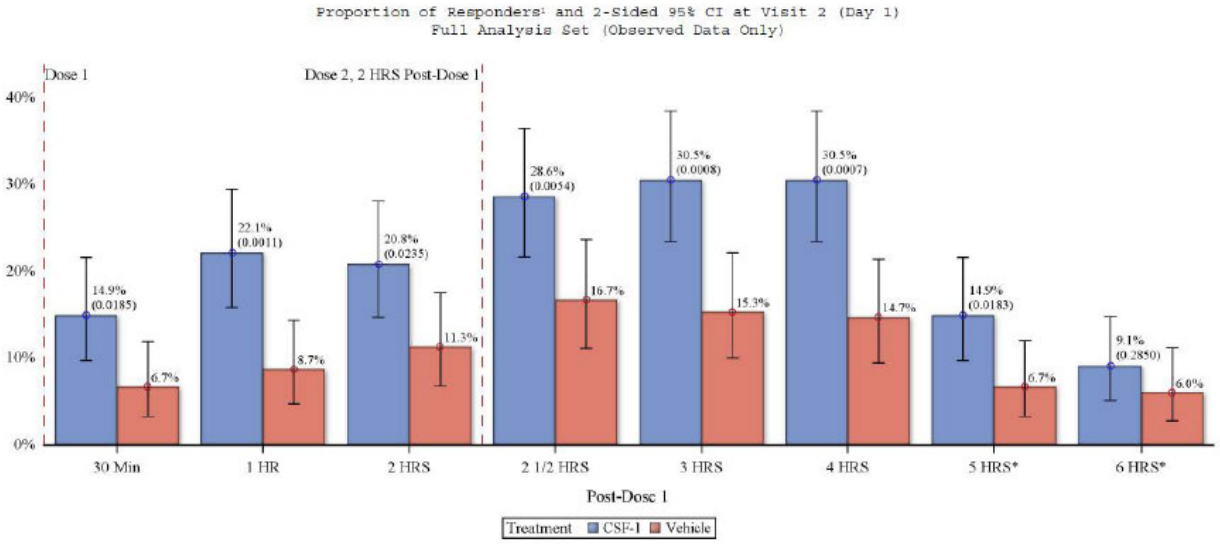
No additional issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

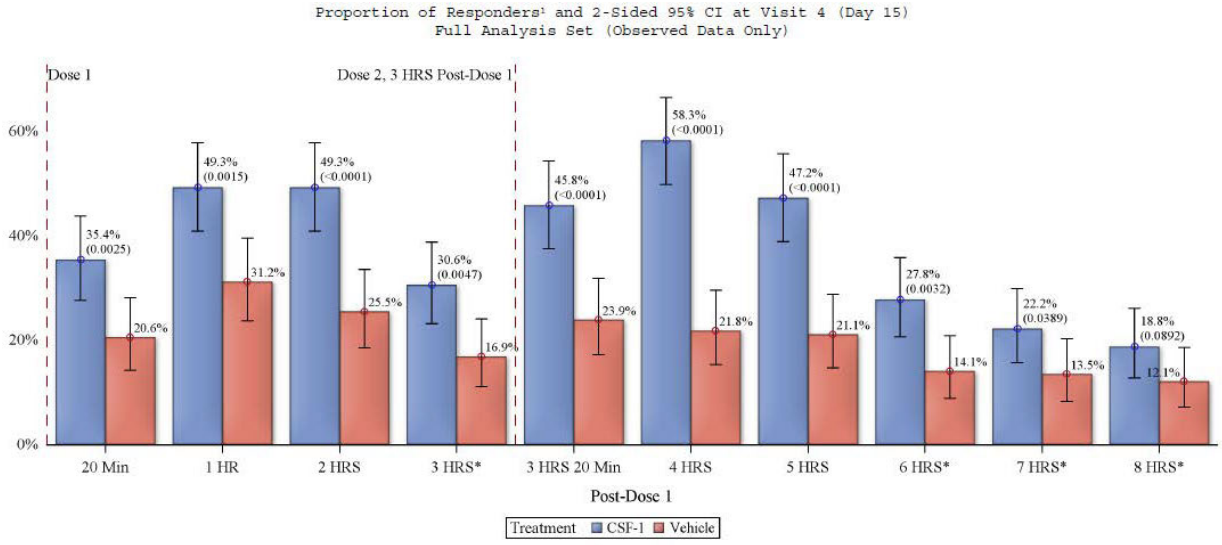
Key Secondary Endpoints

The key secondary endpoints 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 at Visit 3 (Day 8) 2 hours post Dose 1, Visit 3 (Day 8) 1 hour post Dose 2 and Visit 3 (Day 8) 2 hours post Dose 2.

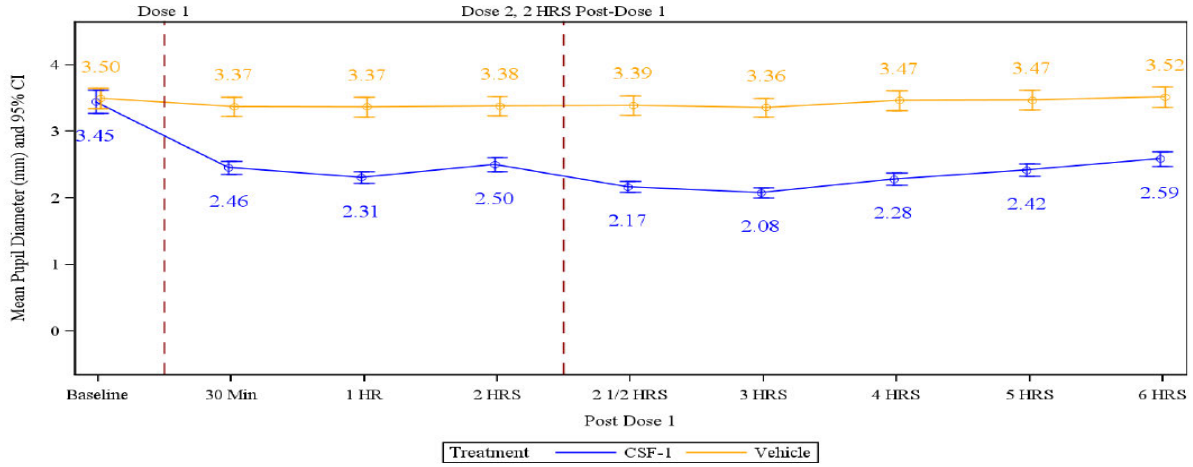
Visit 2 (Day 1): Other Secondary Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS Observed Data Only)



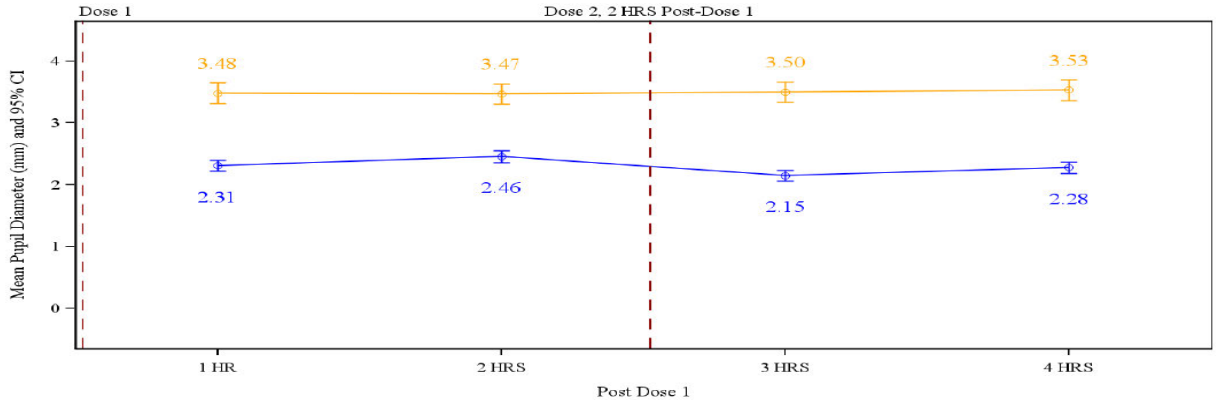
Visit 4 (Day 15): Other Secondary Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS Observed Data Only)



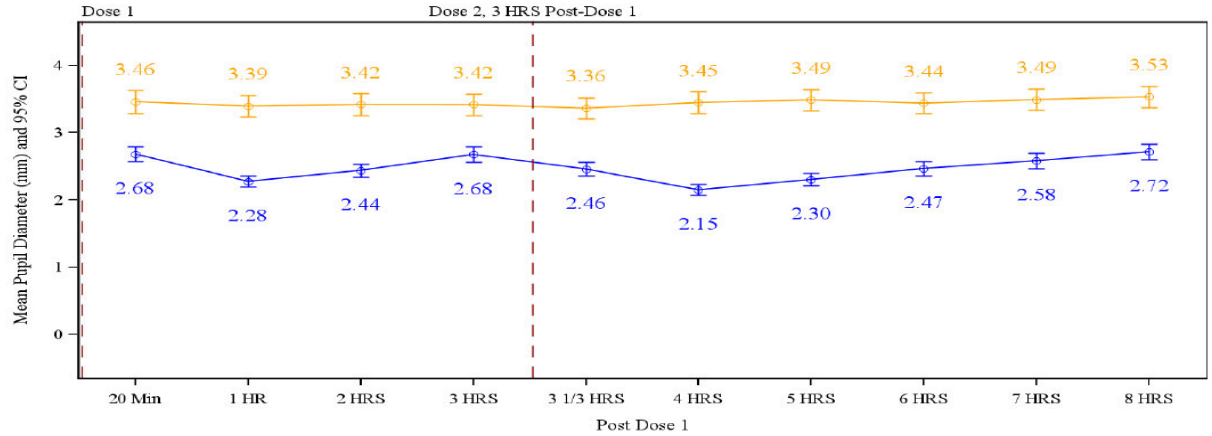
Visit 2 (Day 1): Mean Pupil Diameter Under Near VA at 40 cm



Visit 3 (Day 8): Mean Pupil Diameter Under Near VA at 40 cm



Visit 4 (Day 15): Mean Pupil Diameter Under Near VA at 40 cm



Analysis of Subjects with 3-Line Improvement of BDCVA at 40 cm and no loss of ≥ 5 letters of BDCVA at 4m at Visit 3 (Day 8)

	NEAR-1		NEAR-2	
	CSF-1 N=155	Vehicle N=154	CSF-1 N=154	Vehicle N=150
Day 8, 2 Hours Post-Dose 1				
Number (%) of Responders	61 (39.4)	26 (16.9)	62 (40.3)	31 (20.7)
Number (%) of Non-Responders	94 (60.6)	128 (83.1)	92 (59.7)	119 (79.3)
Treatment Comparisons				
Odds Ratio	3.035		2.807	
95% CI of Odds Ration	(1.736, 5.305)		(1.655, 4.762)	
p-value	<0.0001		0.0001	
Day 8, 1 Hour Post-Dose 2				
Number (%) of Responders	74 (47.7)	24 (15.6)	80 (51.9)	25 (16.7)
Number (%) of Non-Responders	81 (52.3)	130 (84.4)	74 (48.1)	125 (83.3)
Treatment Comparisons				
Odds Ratio	4.751		6.002	
95% CI of Odds Ration	(2.694, 8.379)		(3.431, 10.499)	
p-value	<0.0001		<0.0001	
Day 8, 2 Hours Post-Dose 2				
Number (%) of Responders	60 (38.7)	23 (14.9)	71 (46.1)	29 (19.3)
Number (%) of Non-Responders	95 (61.3)	131 (85.1)	83 (53.9)	121 (80.7)
Treatment Comparisons				
Odds Ratio	3.422		4.161	
95% CI of Odds Ration	(1.923, 6.090)		(2.404, 7.204)	
p-value	<0.0001		<0.0001	

Reviewer Comment:
At all visits and time points assessed, subjects randomized to the CSF-1 group had higher odds of achieving a ≥ 3-line (15-letters) improvement in monocular BDCVA at 40 cm with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m).

Durability of Response

Analysis of Subjects with 3-Line Improvement of BDCVA at 40 cm and no loss of ≥ 5 letters of BDCVA at 4m at Visit 4 (Day 15)

	NEAR-1		NEAR-2	
	CSF-1 N=155	Vehicle N=154	CSF-1 N=154	Vehicle N=150
Day 15, 20 mins Post-Dose 1				
Number (%) of Responders	45/146 (30.8)	26/147 (17.7)	51 (35.4)	29 (20.6)
Number (%) of Non-Responders	101/146 (69.2)	121/147 (82.3)	93 (64.6)	112 (79.4)
Treatment Comparisons				
Odds Ratio	1.948		2.343	
95% CI of Odds Ration	(1.114, 3.408)		(1.349, 4.070)	
p-value	0.0194		0.0025	
Day 15, 1 Hour Post-Dose 1				
Number (%) of Responders	68/146 (46.6)	33/147 (22.4)	71 (49.3)	44 (31.2)
Number (%) of Non-Responders	78/146 (53.4)	114/147 (77.6)	73 (50.7)	97 (68.8)
Treatment Comparisons				
Odds Ratio	2.879		2.205	
95% CI of Odds Ration	(1.720, 4.817)		(1.354, 3.589)	
p-value	<0.0001		0.0015	
Day 15, 2 Hours Post-Dose 1				
Number (%) of Responders	69/146 (47.3)	31/147 (21.1)	71 (49.3)	36 (25.5)
Number (%) of Non-Responders	77/146 (52.7)	116/147 (78.9)	73 (50.7)	105 (74.5)
Treatment Comparisons				
Odds Ratio	3.220		3.022	
95% CI of Odds Ration	(1.908, 5.433)		(1.813, 5.037)	
p-value	<0.0001		<0.0001	
Day 15, 3 Hours Post-Dose 1				
Number (%) of Responders	46/146 (31.5)	18/147 (12.2)	44 (30.6)	24 (16.9)
Number (%) of Non-Responders	100/146 (68.5)	129/147 (87.8)	100 (69.4)	118 (83.1)
Treatment Comparisons				
Odds Ratio	3.129		2.286	
95% CI of Odds Ration	(1.694, 5.780)		(1.288, 4.058)	
p-value	0.0003		0.0047	
Day 15, 20 mins Post-Dose 2				
Number (%) of Responders	69/146 (47.3)	37/147 (25.2)	66 (45.8)	34 (23.9)
Number (%) of Non-Responders	77/146 (52.7)	110/147 (74.8)	78 (54.2)	108 (76.1)
Treatment Comparisons				
Odds Ratio	2.544		2.911	
95% CI of Odds Ration	(1.542, 4.197)		(1.730, 4.900)	

p-value	0.0003		<0.0001	
Day 15, 1 Hour Post-Dose 2				
Number (%) of Responders	75/146 (51.4)	37/147 (25.2)	84 (58.3)	31 (21.8)
Number (%) of Non-Responders	71/146 (48.6)	110/147 (74.8)	60 (41.7)	111 (78.2)
Treatment Comparisons				
Odds Ratio	3.039		5.449	
95% CI of Odds Ration	(1.849, 4.995)		(3.196, 9.290)	
p-value	<0.0001		<0.0001	
Day 15, 2 Hours Post-Dose 2				
Number (%) of Responders	69/146 (47.3)	23/147 (15.6)	68 (47.2)	30 (21.1)
Number (%) of Non-Responders	77/146 (52.7)	124/147 (84.4)	76 (52.8)	112/142 (78.9)
Treatment Comparisons				
Odds Ratio	4.676		3.508	
95% CI of Odds Ration	(2.675, 8.174)		(2.070, 5.943)	
p-value	<0.0001		<0.0001	
Day 15, 3 Hours Post-Dose 2				
Number (%) of Responders	45/146 (30.8)	12/147 (8.2)	40 (27.8)	20 (14.1)
Number (%) of Non-Responders	101/146 (69.2)	135/147 (91.8)	104 (72.2)	122 (85.9)
Treatment Comparisons				
Odds Ratio	4.795		2.496	
95% CI of Odds Ration	(2.393, 9.608)		(1.359, 4.584)	
p-value	<0.0001		0.0032	
Day 15, 4 Hours Post-Dose 2				
Number (%) of Responders	37/146 (25.3)	12/147 (8.2)	32 (22.2)	19 (13.5)
Number (%) of Non-Responders	109/146 (74.7)	135/147 (91.8)	112 (77.8)	122 (86.5)
Treatment Comparisons				
Odds Ratio	3.611		1.950	
95% CI of Odds Ration	(1.775, 7.347)		(1.035, 3.675)	
p-value	0.0004		0.0389	
Day 15, 5 Hours Post-Dose 2				
Number (%) of Responders	30/146 (20.5)	10/147 (6.8)	27 (18.8)	17 (12.1)
Number (%) of Non-Responders	116/146 (79.5)	137/147 (93.2)	117 (81.3)	124 (87.9)
Treatment Comparisons				
Odds Ratio	3.324		1.784	
95% CI of Odds Ration	(1.545, 7.152)		(0.915, 3.477)	
p-value	0.0021		0.0892	

Reviewer's Comment:
In NEAR-1, at Day 15, the treatment effect seems to peak at 1 hour and 2 hours post-dose one and at 1 hour, 2 hours and 3 hours post-dose two timepoints. By hour 3 post-dose one and hour 4 post-dose 2, there is a decrease in treatment effect.

In NEAR-2, at Day 15, the treatment effect seems to peak at 2 hours post-dose one and at 1 hour and 2 hours post-dose two timepoints. By hour 3 post-dose one and hour 3 post-dose 2, there is a decrease in treatment effect.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Studies NEAR 1 and NEAR 2, demonstrated efficacy in their primary endpoints.

Subpopulations
Subgroup analyses for the percentage of subjects with a ≥ 3-line (15-letter) gain from baseline in BDCVA at 40 cm and no loss in BDCVA ≥ 5 letters at 4 m at all 4 time points of Visit 3, Day 8 (primary and key secondary efficacy endpoints) included age group (between 45 and < 55 years, and between 55 to 64 years), baseline BDCVA at 40 centimeters (logMAR ≤ 0.5 and logMAR > 0.5) iris color (brown and light), and baseline MRSE (-4.5 to < -0.5D and -0.5 to +0.75D).

No clinically relevant or statistically significant differences were seen based on the subgroup analyses.

8. Review of Safety

8.1. Safety Review Approach

The studies which provide the main support for safety were: NEAR-1 (20-150-0002), NEAR-2 (20-150-0003) and 21-150-0005. On 4/20/23 (SDN-10), a 120-day Safety Update was submitted. This submission included information from the completed long term safety study 21-150-0005.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

NEAR-1 (20-150-0002): Extent of Exposure (Safety Population)

	NEAR-1		NEAR-2	
	CSF-1 (N=155)	Vehicle (N=154)	CSF-1 (N=153)	Vehicle (N=151)
Treatment exposure (days)				
Mean (SD)	14.3 (3.1)	14.6 (2.8)	14.4 (3.5)	14.9 (3.2)
Median	15	15	15	15
Min, Max	1, 19	1, 22	1, 28	1, 24
Number of subjects with treatment exposure by week, n (%)				
<2 weeks	131 (84.5%)	129 (83.8%)	122 (79.7%)	113 (74.8%)
2 to < 6 weeks	24 (15.5%)	25 (16.2%)	31 (20.3%)	38 (25.2%)

21-150-0005: Extent of Exposure (Safety Population)

	CSF-1 (N=118)	Vehicle (N=60)
Treatment exposure (days)		
Mean (SD)	67.6 (34.9)	59.4 (39.9)
Median	49	45
Min, Max	1, 152	1, 153
Number of subjects with treatment exposure by week, n (%)		
<2 weeks	4 (3.4%)	6 (10.0%)
2 to < 6 weeks	19 (16.1%)	19 (31.7%)
6 to < 12 weeks	66 (55.9%)	22 (36.7%)
12 to < 18 weeks	22 (18.6%)	8 (13.3%)
18 to < 21 weeks	6 (5.1%)	4 (6.7%)
≥ 21 weeks	1 (0.8%)	1 (1.7%)

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review.

8.3.2. Categorization of Adverse Events

Safety of CSF-1 was assessed by monitoring treatment-emergent adverse events (TEAEs, ocular/non-ocular), serious AEs, ophthalmic assessments and clinical laboratory evaluations. AEs were classified by MedDRA system organ class (SOC) 23.1.

8.3.3. Routine Clinical Tests

The routine clinical testing to evaluate the safety concerns (i.e., biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials for this product.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in NEAR-1, NEAR-2 or Study 21-150-0005. One death occurred in Study 18-150-0006. The subject was randomized to the pilocarpine HCl group. The subject experienced a non-ocular SAE of coronary artery disease. Action was taken with the study drug and was reported as drug withdrawn. The SAE resulted in death. The SAE was rated severe.

8.4.2. Serious Adverse Events

There were no ocular SAEs reported in NEAR-1 or NEAR-2. There was 1 non-ocular SAE of enteritis in a subject in the vehicle arm of NEAR-1 and 1 non-ocular SAE of arthritis infective in a subject in the vehicle arm of NEAR-2. No SAEs were reported in Study 21-150-0005.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

NEAR-1 (20-150-0002): Discontinuations

Subject (b) (6)	Group	Description
	Vehicle	Discontinued from study for TEAE of enteritis which was of severe intensity and resolved by study exit.
	CSF-1	Discontinued from study for TEAE of periocular pressure, dry mouth and nausea upon installation which were of moderate intensity and resolved by study exit.
	CSF-1	Discontinued from study for TEAE of headache, nausea and vomiting which were of mild intensity and resolved by study exit.
	CSF-1	Discontinued from the study for TEAE of blurred vision and right and left brow ache that occurred within 30 minutes of IP which were mild in intensity and resolved by study exit.
	CSF-1	Discontinued from the study for TEAE of metamorphopsia which was mild in intensity and resolved by study exit.

NEAR-2 (20-150-0003): Discontinuations

Subject (b) (6)	Group	Description
	CSF-1	Discontinued from study for TEAE of COVD-19 which was of mild intensity and resolved by study exit.
	CSF-1	Discontinued from the study for TEAE of subjective complaint of restricted visual field. This AE was considered moderate in intensity and was resolving by study exit.
	Vehicle	Discontinued from the study for TEAE of pigment epithelial detachment (mild and resolving by study exit) and scabies (moderated and resolved study exit).

Study 21-150-0005: Discontinuations

Subject (b) (6)	Group	Description
	CSF-1	Discontinued from study for TEAE of continuous irritation which was of mild intensity and resolved by study exit.
	Vehicle	Discontinued from study for TEAE of blurred vision which was of mild intensity and resolved by study exit.
	Vehicle	Discontinued from study for TEAE of retinal tear and was ongoing at time of study exit.
	CSF-1	Discontinued from the study for TEAE of headache which was mild in intensity and resolved by study exit.
	Vehicle	Discontinued from the study for TEAE of headache which was moderate in intensity and resolved by study exit.

8.4.4 Treatment Emergent Adverse Events and Adverse Reaction

Ocular Treatment Emergent Adverse Events occurring in ≥ 1% subjects in the CSF-1 treatment group

System Organ Class (SOC) Preferred Term (PT)	NEAR-1		NEAR-2		Study 21-150-0005		Integrated Data[1]	
	CSF-1 (N=155)	Vehicle (N=154)	CSF-1 (N=153)	Vehicle (N=151)	CSF-1 (N=118)	Vehicle (N=60)	CSF-1 (N=426)	Vehicle (N=365)
Any Ocular TEAEs	17 (11%)	6 (4%)	43 (28%)	18 (12%)	43 (36%)	17 (28%)	89 (21%)	35 (10%)
Instillation site pain	9 (6%)	1 (0.6%)	9 (6%)	0	21 (18%)	0	34 (8%)	1 (0.3%)
Vision blurred*	2 (1%)	0	14 (9%)	2 (1%)	10 (8%)	5 (8%)	25 (6%)	7 (2%)
Conjunctival hyperemia	0	0	5 (3%)	1 (0.7%)	2 (2%)	3 (5%)	6 (1%)	2 (0.5%)
Instillation site pruritus	1 (0.6%)	0	3 (2%)	1 (0.7%)	1 (0.8%)	1 (2%)	5 (1%)	2 (0.5%)
Vitreous detachment	1 (0.6%)	0	1 (0.7%)	0	4 (4%)	1	3 (0.7%)	0
Photophobia	1 (0.6%)	0	2 (1%)	0	1 (0.8%)	0	4 (1%)	0
Blepharitis	0	0	1 (0.7%)	1 (0.7%)	2 (2%)	2 (3%)	1 (0.2%)	3 (1%)
Conjunctival papillae	0	0	0	0	3 (3%)	4 (7%)	3 (0.7%)	2 (0.5%)
Eye discharge	0	1 (0.6%)	1 (0.7%)	2 (1%)	1 (0.8%)	0	3 (0.7%)	3 (1%)
Conjunctival hemorrhage	1 (0.6%)	0	2 (1%)	0	0	0	2 (0.5%)	0
Eye irritation	0	0	2 (1%)	1 (0.7%)	0	0	2 (0.5%)	1 (0.3%)
Instillation site irritation	0	0	1 (0.7%)	0	1 (0.8%)	0	2 (0.5%)	0
Photopsia	0	0	2 (1%)	0	0	0	2 (0.5%)	0
Punctate keratitis	0	0	2 (1%)	1 (0.7%)	0	1 (2%)	2 (0.5%)	2 (0.5%)

Note: N in the header is the number of subjects from the Safety Set in that treatment arm and is the denominator for percentages. A TEAE is defined as an AE that started or worsened in severity or frequency after the first dose of study drug. All AEs are medically coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Subjects reporting multiple PTs or SOCs are counted only once within that SOC.

* Includes 'vision blurred' and 'visual impairment'.

Source: 120-Day Safety Update, Table 11. Table 14.3.1.2.1.1 and Table 14.3.1.2.1.2

Reviewer's comment:

The TEAEs reported for ≥ 1% in either treatment group, in order of descending incidence, were: instillation site pain (6%), blurred vision (4%), conjunctival hyperemia (2%), instillation site pruritis (1%), visual impairment (1%), and conjunctival hemorrhage (1%).

The TEAEs reported for ≥ 1% in either treatment group, in order of descending incidence, were: instillation site pain, blurred vision, visual impairment, conjunctival papillae, conjunctival hyperemia, vitreous detachment, blepharitis, eye naevus, and telangiectasia.

Non-Ocular Treatment Emergent AEs Occurring in ≥ 1% of Subjects

System Organ Class (SOC) Preferred Term (PT)	NEAR-1		NEAR-2		Study 21-150-0005 2 Weeks		Integrated Data	
	CSF-1 (N=155)	Vehicle (N=154)	CSF-1 (N=153)	Vehicle (N=151)	CSF-1 (N=118)	Vehicle (N=60)	CSF-1 (N=426)	Vehicle (N=365)
Any Non-Ocular TEAEs	13 (8%)	8 (5%)	26 (17%)	9 (6%)	22 (19%)	10 (16%)	53 (12%)	19 (5%)
Headache	8 (5%)	2 (1%)	15 (10%)	2 (1%)	4 (3%)	2 (3%)	27 (6%)	5 (1%)
Brow ache*	2 (1%)	0	4 (3%)	1 (1%)	2 (2%)	0	8 (2%)	1 (0.3%)
Nausea	4 (3%)	2 (1%)	1 (1%)	0	1 (1%)	0	6 (1%)	2 (0.5%)

Note: N in the header is the number of subjects from the Safety Set in that treatment arm and is the denominator for percentages. A TEAE is defined as an AE that started or worsened in severity or frequency after the first dose of study drug. All AEs are medically coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Subjects reporting multiple PTs or SOCs are counted only once within that SOC TEAEs

*Includes preferred terms 'instillation site pain' and 'facial pain'

Source: 120-Day Safety Update, Table 13. Table 14.3.1.3.1.1 and Table 14.3.1.3.1.2

Reviewer's comment:
Headache was reported by 27 subjects (6%) in the CSF-1 group and in 5 subjects (1%) in the Vehicle group. Nausea was reported in 6 subjects (1.4%) in the CSF-1 group and 2 subjects (0.5%) in the Vehicle group. Instillation site pain and facial pain were reported in 8 subjects (2%) in the CSF-1 group and 1 subject (0.3%) in the Vehicle group.

The prolonged treatment in Study 21-150-0005 showed that most of the non-ocular TEAEs reported with CSF-1 occurred within the first 2 weeks of treatment. 3.4% of subjects in Study 21-150-0005 treated with CSF-1 reported headache during the first 2 weeks of treatment, while no subject reported it during the period beyond 2 weeks.

8.4.4. Laboratory Findings

No clinically significant differences in hematology, blood chemistry, or urinalysis were observed between the treatment groups.

8.4.5. Vital Signs

Small shifts in vital signs were observed, but no trends or differences between treatment groups were identified.

8.4.6. Electrocardiograms (ECGs)

Electrocardiograms were not assessed during this development program.

8.4.7. Immunogenicity

Immunogenicity was not assessed during this development program.

8.5. Additional Safety Explorations

8.5.1. Pediatrics and Assessment of Effects on Growth

The Applicant requested a full waiver for pediatric subjects 0 to 17 years of age because studies are impossible or highly impracticable. Presbyopia is included on the automatic waiver list as a condition that is rare in pediatric patients.

At the PeRC meeting on 9/12/23, PeRC agreed with granting the full waiver for pediatric subjects 0 to 17 years of age because studies would be impossible or highly impractical as there are too few patients to study.

8.5.2. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Pilocarpine is a non-narcotic and does not have abuse potential.

8.6. Safety in the Postmarket Setting

8.6.1. Safety Concerns Identified Through Postmarket Experience

Pilocarpine ophthalmic solution 0.4% is not a marketed drug product. There are no Postmarketing data to report.

8.7. Integrated Assessment of Safety

The safety database contained in this submission establishes the safety of pilocarpine ophthalmic solution 0.4%.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application. There were no issues identified in the review of the application that were thought to benefit from an Advisory Committee discussion.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The application for NDA 217836 Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4% for the treatment of presbyopia in adults is recommended for approval with the attached draft labeling in Appendix 13.3 of this review. This is still draft labeling. For final labeling, see the CDTL Summary memo.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting

of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): NEAR-1 (20-150-0002)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NEAR-2 (20-150-0003)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 19		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 21-150-0005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b),		

(c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3 Labeling

NDA 217836 is recommended for approval with the draft labeling revisions found below. The application for NDA 217836 Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4% for the treatment of presbyopia in adults is recommended for approval with the attached draft labeling. For final labeling, see the CDTL Summary memo.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER M HAMMER
10/02/2023 01:49:22 PM

RHEA A LLOYD
10/02/2023 01:53:01 PM