CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217836Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader, Deputy Division Director, Division Director Summary Review of NDA 217836

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, M.D., William Boyd, M.D., Wiley Chambers, M.D.
Subject	Summary Review
NDA #	217836
IND #	131464
Applicant	Orasis Pharmaceuticals, Inc.
Date of Submission	December 22, 2022
PDUFA Goal Date	October 22, 2023
Proprietary Name	Qlosi
Established or Proper Name	Pilocarpine ophthalmic solution, 0.4%
Dosage Form(s)	Topical
Indication	Treatment of presbyopia in adults
Dosing Regimen	Instill one drop OU bid
Regulatory Action	**APPROVAL**

NDA 217836 Review Team Role	Reviewer
OND RPM	Jacqueline Smith
CDTL	Rhea Lloyd
Clinical Reviewer	Jenna Hammer
Nonclinical Reviewer	Erin Ruhland/ Mukesh Summan
ATL	Chunchun Zhang
Drug Substance	Daniel Jansen/ Zhengfu Wang
Drug Product	Anne Marie Russell/ Danae Christodolou
Manufacturing/ Facilities/ Process	Kejun Cheng/ Aditi Thakur
OPQ Microbiology	Sallie Crenshaw/ John Metcalfe
Statistical Reviewer	Chungfen Ren / Greg Soon
Regulatory Business Process Manager	Shazma Aftab
Clinical Pharmacology Reviewer	Sneha Dhapare / Ji Ping
OND Labeling Reviewer	Derek Alberding
OSE RPM	Oyinlola Fashina
DMEPA Team Lead	Valerie Vaughan
DMEPA Reviewer	Sofanit Getahun
OSI Lead	Michelle Fedowitz
OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer

Administrative Background

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 enhance the depth of focus and improve near and intermediate 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.

Qlosi (pilocarpine ophthalmic solution) 0.4% was developed by Orasis Pharmaceuticals, LLC. Orasis Pharmaceuticals has submitted 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 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.

The clinical development program was conducted under IND 131464 for pilocarpine ophthalmic solution 0.4% in support of this application and included 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.

The NDA 217936 for Qlosi (pilocarpine ophthalmic solution) 0.4% will be approved for the treatment of presbyopia in adults.

Benefit-Risk 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 and 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 benefits of pilocarpine hydrochloride ophthalmic solution 0.4% OU bid in treating patients with presbyopia outweigh the potential risks to patients with presbyopia.

Benefit-Risk Dimensions

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.
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.

Product Quality

From the Integrated Quality Assessment finalized on September 1, 2023:

Composition of Pilocarpine Ophthalmic Solution 0.4% (Formulation 3, Final)

Excipients	Concentration		Function	Quality Standard
	mg/mL	%w/v		
Pilocarpine hydrochloride	4.0	0.4	Drug substance	USP-NF
Hypromellose (b) (4)	(b) (4)			USP-NF
Sodium chloride				USP-NF
Sodium hyaluronate				Ph.Eur.
Disodium edetate				USP-NF
(b) (4) Sodium hydroxide and/or Hydrochloric acid	q.s.		pH adjuster	USP-NF
Water for Injection	(b) (4)			USP-NF

NF = National Formulary; USP = United States Pharmacopoeia; q.s. = as much as suffices, Ph. Eur. = European Pharmacopoeia

Drug Product Specifications for Pilocarpine 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
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 detem1ination 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.

Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)	(b) (4)	(b) (4)	Approve - Based on Previous History
			Approve - Based on PAI
			No Evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary
			No Evaluation Necessary

OPQ Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process, and quality microbiology aspects. The product is regulated as a drug and device combination product per the Genus decision. However, this single dose (b) (4) vial was considered low risk and CDRH confirmed that a CDRH consult is not necessary on 1/13/2023.

From the Integrated Quality Assessment Review dated September 29, 2023:
NDA 217836, Pilocarpine hydrochloride ophthalmic solution, 0.4% was originally recommended for Complete Response because the facilities compliance status was not acceptable, refer to IQA #1 dated Sep 1, 2023. The drug product manufacturing site, [redacted] (b) (4) was initially out of compliance (pOAI) in recent PAI. A surveillance inspection occurred from [redacted] (b) (4) and it was found acceptable based on review of the findings from the inspection, including the firm responses and other considerations as applicable on 9/26/2023. All other facilities are found acceptable based on profile review and inspectional history. Therefore, OPMA issued an overall recommendation of "Approve" on September 27, 2023. All the other OPQ disciplines uphold the approval recommendation. Therefore, **NDA 217836 is recommended for approval from product quality perspective.**

Nonclinical Pharmacology/Toxicology

From the Nonclinical review dated 9/8/23: All nonclinical elements of the NDA were either 1) referenced from NDA 020237 (Salagen) with the Applicant obtaining right of reference from the NDA holder for those studies, or 2) provided through the conduct of GLP studies. The NDA is approvable from a Nonclinical Pharmacology/Toxicology perspective.

Brief Discussion of Nonclinical Findings

- For nonclinical systemic safety, pharmacology and drug metabolism, the Applicant has obtained right of reference for NDA 020237 (Salagen).
- Salagen labeling has not undergone PLLR conversion, however most information required by guidance for the PLLR formatted label for this application are present in the Salagen labeling.
- The Applicant provided a nonclinical chronic ocular toxicity study to support ocular safety of the formulation and a 28-day ocular toxicity study to support qualification of impurities.
- No adverse toxicity was associated with the Applicant's formulation or the qualified impurities. These studies are adequate for approval.

Clinical Pharmacology

From the Clinical Pharmacology review dated 8/8/23:

Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness comes from two Phase 3 studies (Study 21-150-0002 (NEAR-1) and Study 21-150-0003 (NEAR-2)) of 15 days duration that assessed as the percentage of responders, i.e., subjects with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm and no loss ≥ 5 letters in BDCVA at 4 m (ETDRS chart) in the study eye. Efficacy data from the Phase 2b study, Study 18-150-0006, provides supportive evidence.
General dosing instructions	Proposed dosing is 1 drop in each eye, which can be repeated 2 to 3 h after the first dose, for an effect up to 8h.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment in any patient subgroups is necessary as it is a local acting drug with limited systemic absorption.

Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical studies as well as the PK study.

Clinical Efficacy

Efficacy Results – Primary Endpoint

NEAR-1 and NEAR-2 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), following Dose 1, 1-hour post-treatment.

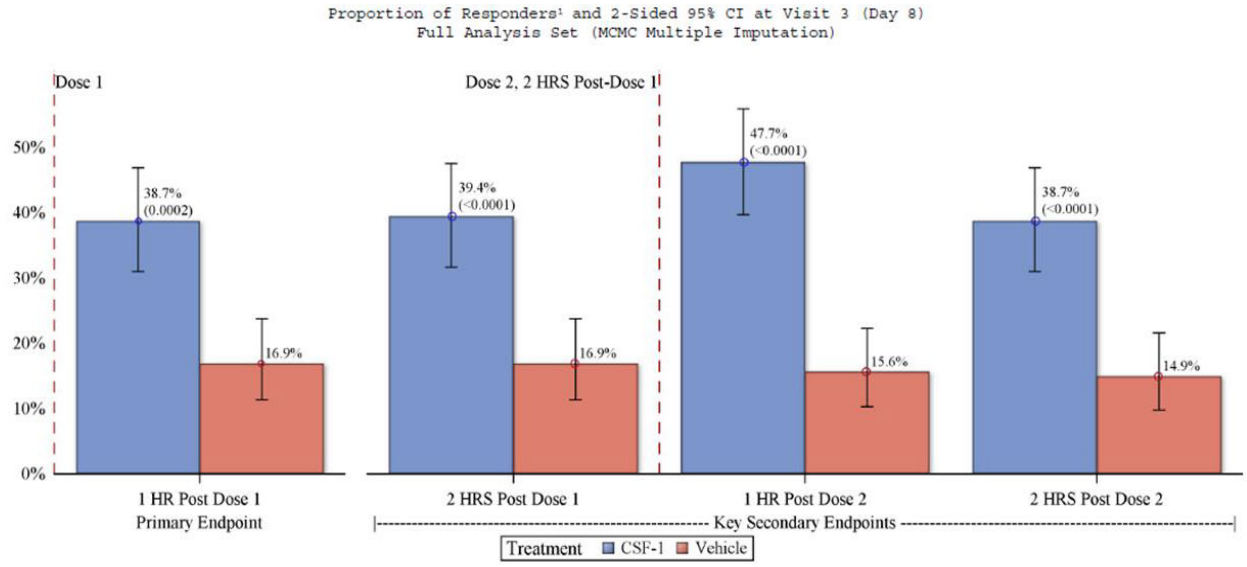
NEAR-1(020-150-0002)

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): Primary Endpoint

	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 Comparison Odds Ratio (CI)	2.92 (1.66, 5.11)	
p-value	0.0002	

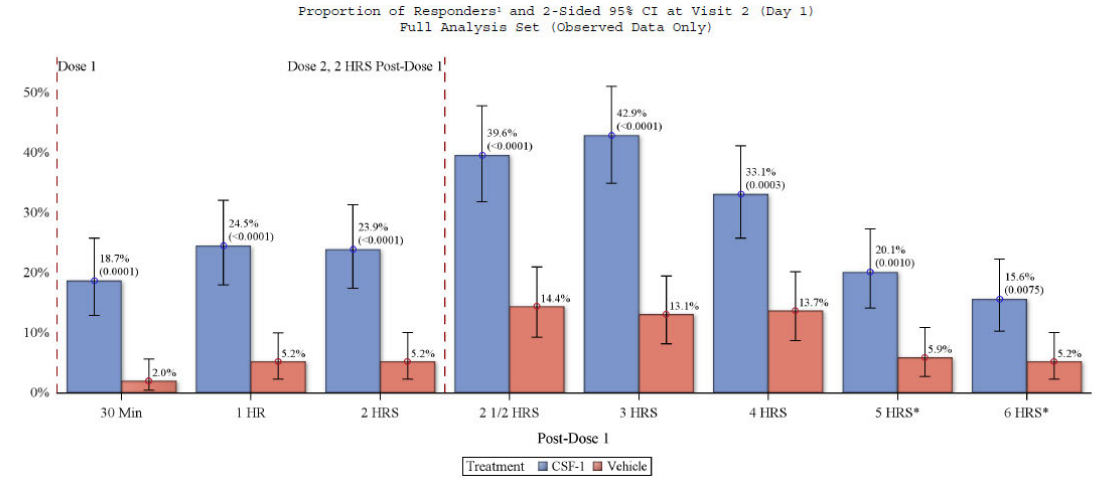
Visit 3 (Day 8): Primary and Key Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS MCMC Multiple Imputation)



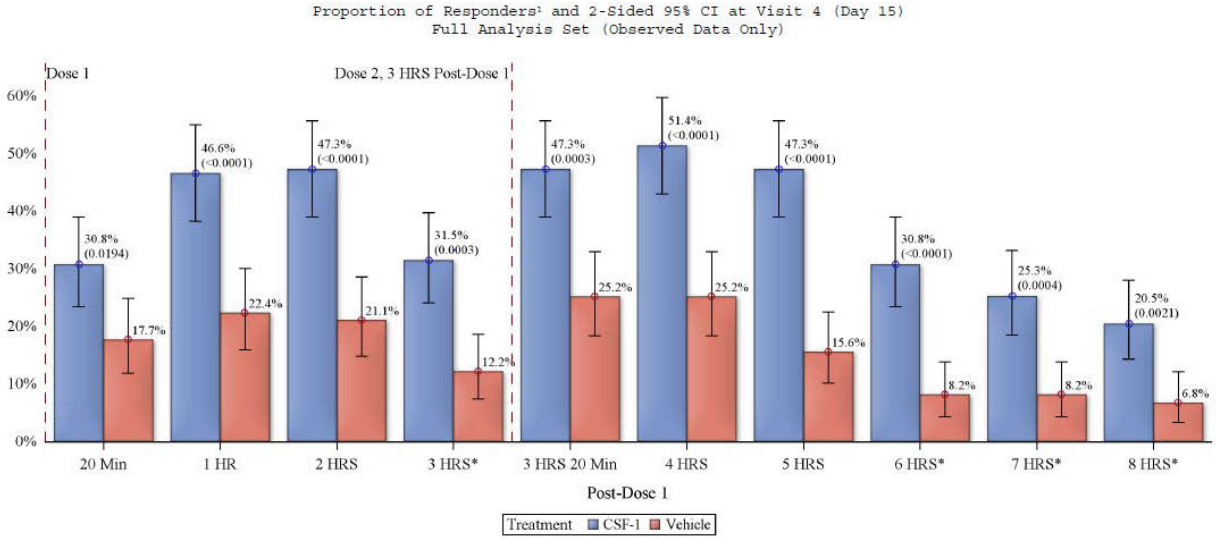
Reviewer's Comment:

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; 39%; p = 0.0002) compared to the Vehicle group (n = 26; 17%).

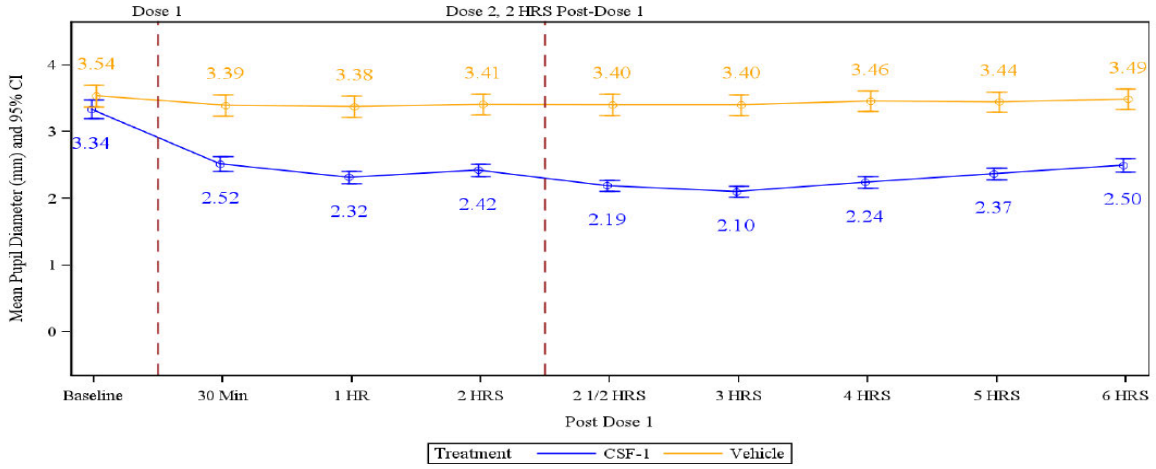
Visit 2 (Day 1): Other Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) at (FAS Observed Data Only)



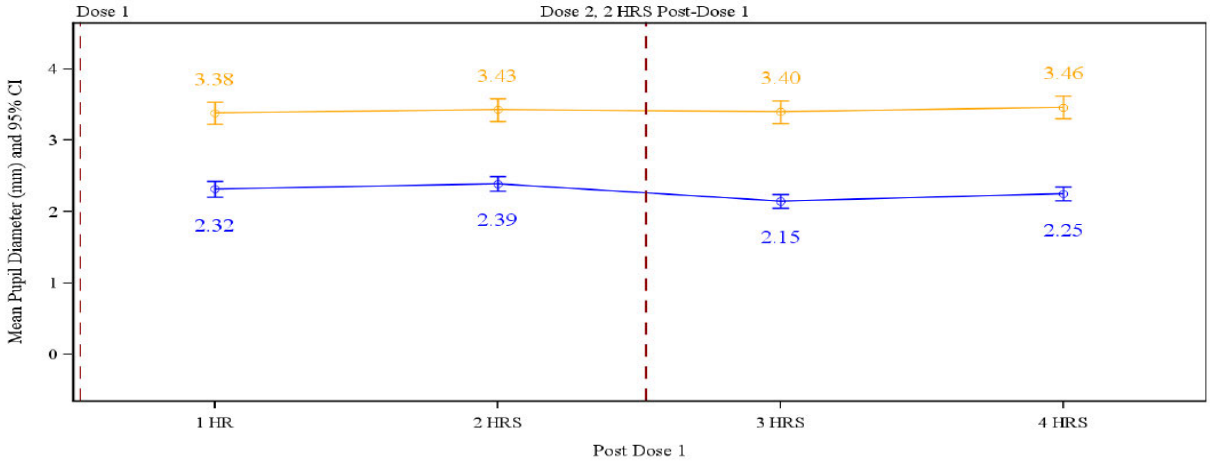
Visit 4 (Day 15): Other Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS Observed Data Only)



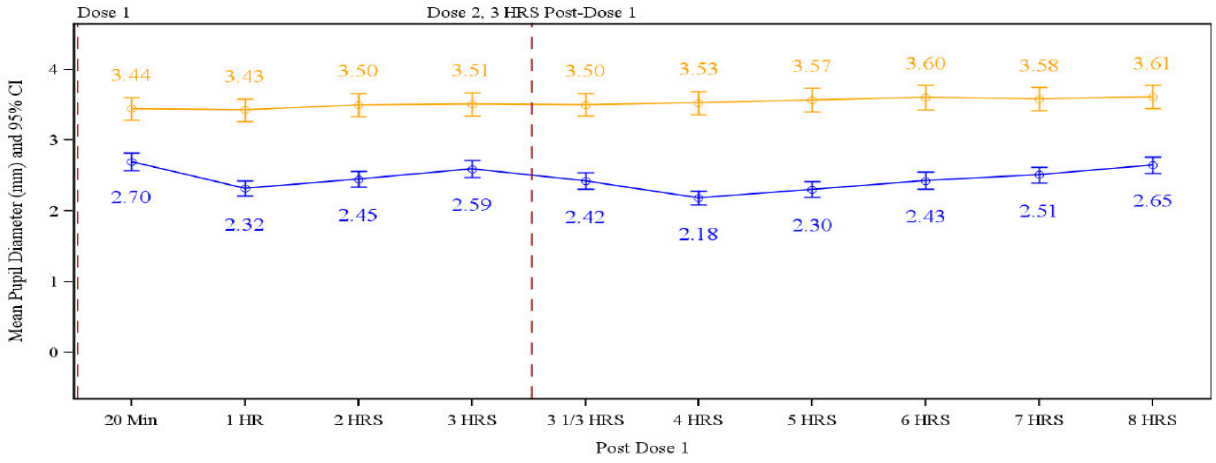
Visit 2 (Day 1): Mean Pupil Diameter Under Near VA at 40 cm



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



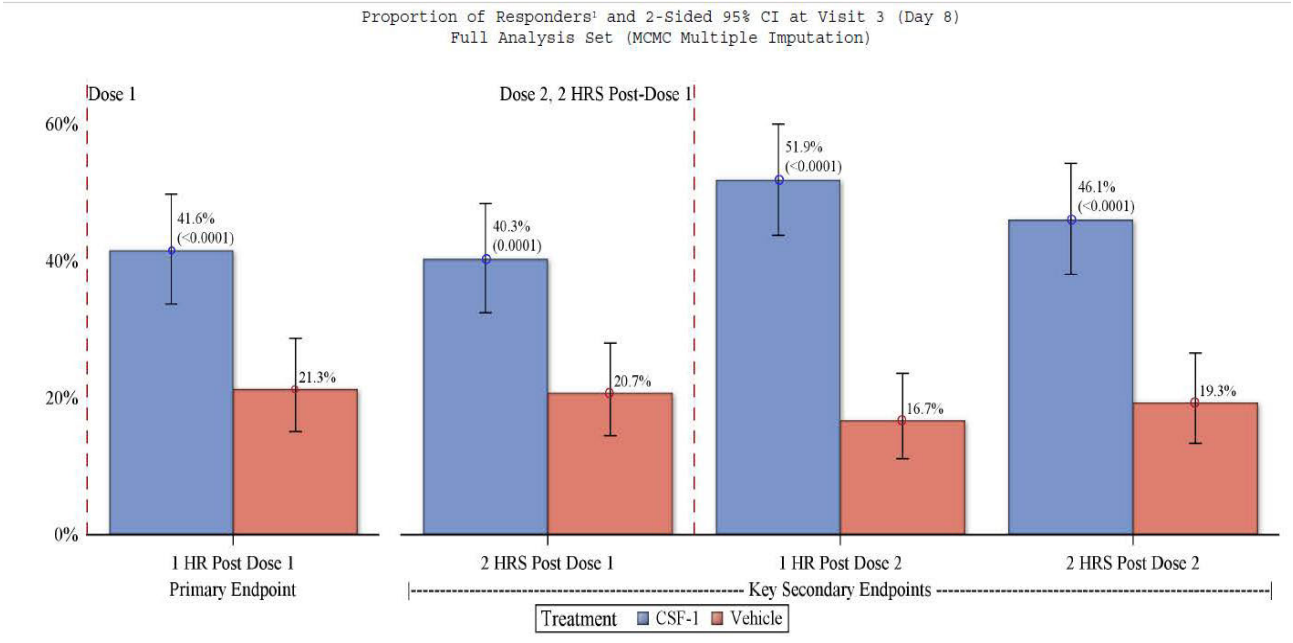
NEAR-2 (020-150-0003)
Missing data due to withdrawal from lack of efficacy was imputed as failure. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs were imputed employing MI using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology. For 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 ≥ 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 comparison Odds Ratio (95% CI)	2.98 (1.75, 5.06)		2.71 (1.56, 4.70)	
p-value	<0.0001		0.0004	

Reviewer's Comment:
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.

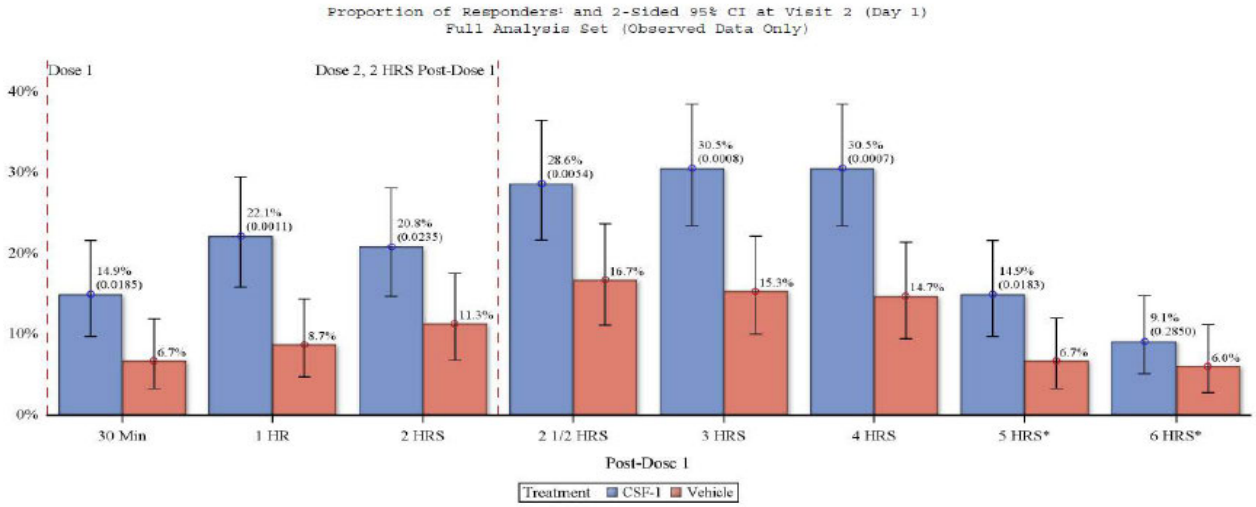
Visit 3 (Day 8): Primary and Key Secondary Endpoints Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS MCMC Multiple Imputation)



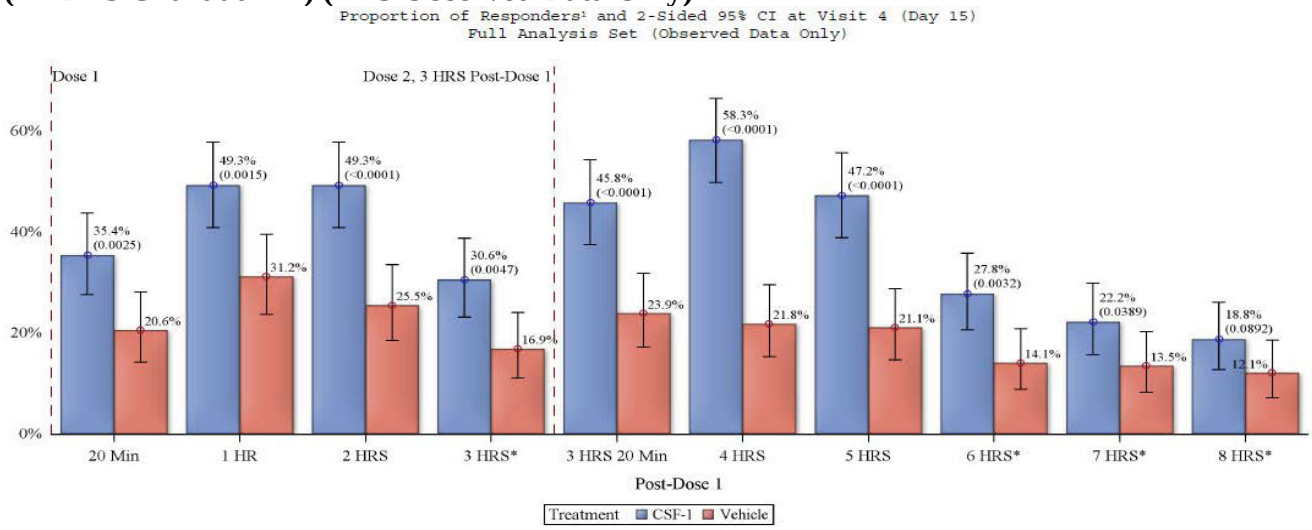
Reviewer's Comment:
In NEAR-2 (020-150-0003), at Visit 3 (Day 8) 1 hour post Dose 1, a statistically significant greater percentage of subjects had improvement of ≥ 3-lines (15-letters) in monocular BDCVA at 40 cm and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) in the CSF-1 group ([n = 64; 42%; p <0.0001,including site #41] and [n=56; 41%; p=0.004, excluding site #41]) compared to the Vehicle group ([n = 32; 21%, including site #41] and [n=30; 22%, excluding site #41]).

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.

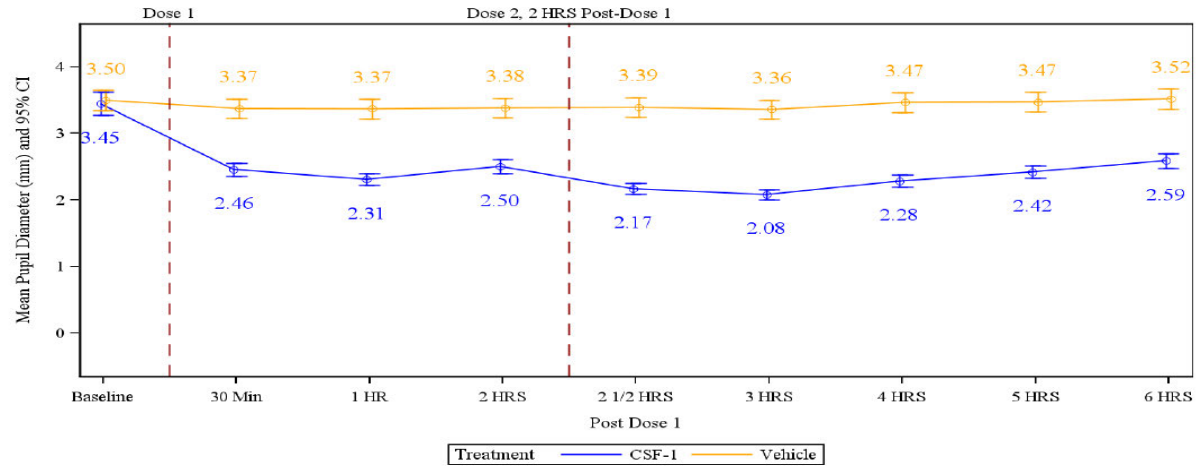
Visit 2 (Day 1): Other Secondary Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS Observed Data Only)



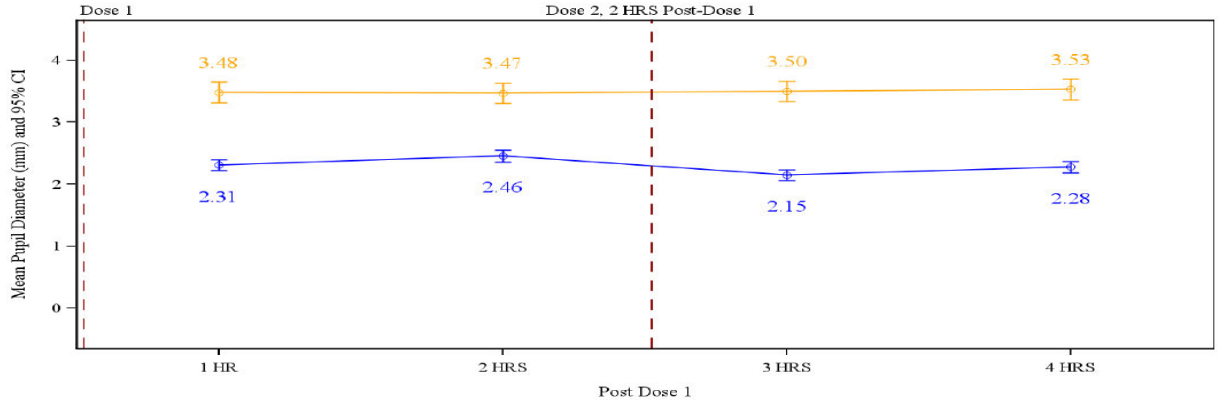
Visit 4 (Day 15): Other Secondary Analysis of Subjects with a ≥ 3-line (15-letter) Gain from Baseline in BDCVA (Precision Vision Chart at 40 cm) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) (FAS Observed Data Only)



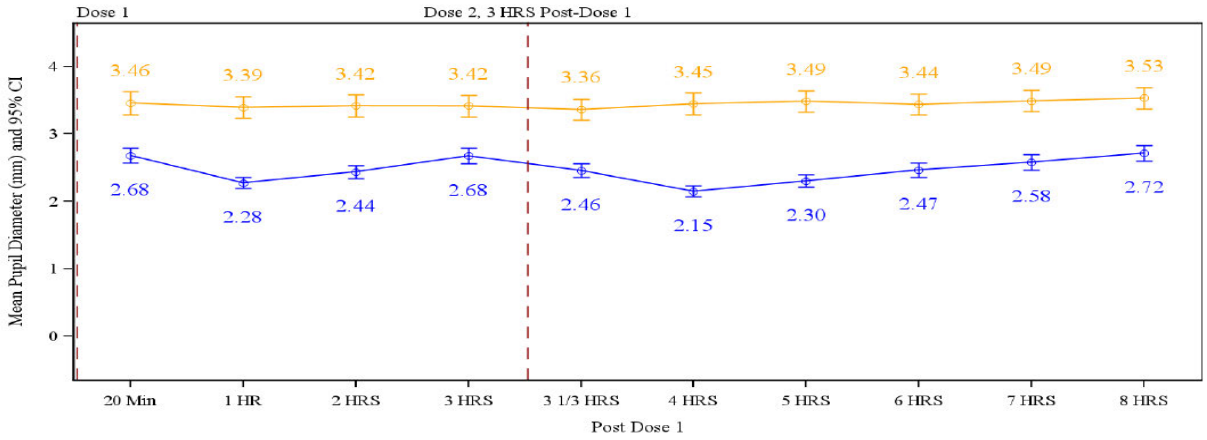
Visit 2 (Day 1): Mean Pupil Diameter Under Near VA at 40 cm



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 comparison Odds Ratio (CI)	3.03 (1.74, 5.30)		2.81(1.66, 4.76)	
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)
Odds Ratio (CI)	4.75 (2.68, 8.38)		6.00 (3.43, 10.50)	
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 comparison Odds Ratio (CI)	3.42 (1.92, 6.09)		4.16 (2.40, 7.20)	
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 Comparisoin Odds Ratio (CI)	1.95 (1.11, 3.41)		2.34 (1.35, 4.07)	
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)
Odds Ratio	2.88 (1.72, 4.82)		2.21 (1.35, 3.59)	
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)

Odds Ratio	3.22 (1.91, 5.43)		3.02 (1.81, 5.04)	
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)
Odds Ratio	3.13 (1.69, 5.78)		2.29 (1.29, 4.06)	
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)
Odds Ratio	2.54 (1.54, 4.20)		2.91 (1.73, 4.90)	
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)
Odds Ratio	3.04 (1.85, 5.00)		5.45 (3.20, 9.30)	
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)
Odds Ratio	4.68 (2.68)		3.51 (2.07, 5.94)	
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)
Odds Ratio	4.80 (2.40, 9.61)		2.50 (1.36, 4.58)	
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)
Odds Ratio	3.61 (1.78, 7.35)		1.95 (1.04, 3.68)	
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)
Odds Ratio	3.32 (1.55, 7.15)		1.78 (0.91, 3.48)	
p-value	0.0021		0.0892	

Reviewer's Comment:
In NEAR-1, at Day 15, with two doses the treatment effect seems to last for 8 hours.

In NEAR-2, at Day 15, with two doses, the treatment effect seems to last for 7 hours.

Safety

Safety Database

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.

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%)

Reviewer's comments:
There was adequate exposure for this indication.

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 and was considered to be not related to the study drug.

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. Both SAEs were considered not related to the study drug. No SAEs were reported in Study 21-150-0005.

Dropouts and/or Discontinuations Due to Adverse Events

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

Subject Number	Group	Description
(b) (6)	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 Number	Group	Description
(b) (6)	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 Number	Group	Description
(b) (6)	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 which was considered not related to study drug 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.

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: 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 the CSF-1 treatment group were: instillation site pain (6%), and blurred vision (4%).

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: A TEAE is defined as an AE that started or worsened in severity or frequency after the first dose of study drug. . 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, brow ache and nausea were reported more frequently in the CSF-1 group then 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.

Biomicroscopy and Fundus Exam
There were no clinically relevant changes in the fundus exam that occurred in either treatment group during the clinical trials.

Vital Signs
No clinically significant differences in hematology, blood chemistry, or urinalysis were observed between the treatment groups. Small shifts in vital signs were observed, but no trends or differences between treatment groups were identified.

Subgroup Analyses by Demographic Group
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.

Advisory Committee Meeting

There were no issues raised during the review of this application that were thought to benefit from an Advisory Committee meeting.

Pediatrics

The Applicant requested a full waiver for pediatric subjects 0 to 17 years of age because studies are impossible or highly impracticable. Presbyopia does not occur in children and is included on the automatic waiver list as a condition that is rare in pediatric patients. At the PeRC meeting on September 12, 2023, 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.

BIOSTATISTICS

From the Statistical Review finalized on 9/5/2023:

Efficacy Results
Orasis used the p-value (NEAR-1: 0.0002; NEAR-2: <0.0001) for comparing the conditional odds of subjects being a responder in CSF-1 group with that in vehicle group to interpret the percentages of responders in both groups. Based on the same logistic regression model and strategies handling the intercurrent events/missing data, we used G-computation approach to estimate the risk differences (NEAR-1: 19.2% [95% CI: 9.5-28.8] ; NEAR-2: 21.9% [95% CI: 11.8-32.0]) and the p-values (both <0.0001 in NEAR-1 and NEAR-2) for comparing risk differences**Error! Reference source not found.**. The Statistical Group recommended using these risk differences with 95% CIs and p-values estimated by G-computation approach to compare the percentages of responders in the CSF-1 and vehicle groups although the p-values are only slightly different.

Visit 3 (Day 8): Primary Efficacy Analysis of Study Eye 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) 1-Hour Post-Dose 1, FAS (MCMC MI)

Parameter statistics	20-150-0002 (NEAR-1)		20-150-0003 (NEAR-2)	
	CSF-1 (N=155)	Vehicle (N=154)	CSF-1 (N=154)	Vehicle (N=150)
Number (%) of responders [a,b]	60 (38.7)	26 (16.9)	64 (41.6)	32 (21.3)
Number (%) of non-responders	95 (61.3)	128 (83.1)	90 (58.4)	118 (78.7)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [c]	2.9 (1.7, 5.1)		3.0 (1.8, 5.1)	
p-value [c]	0.0002		<0.0001	
Risk difference (%, 95% CI) [d]	19.2 (9.5, 28.8)		21.9 (11.8, 32.0)	
p-value [d]	<0.0001		<0.0001	

Abbreviations: BDCVA = best distance corrected visual acuity; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study; MCMC = Markov Chain Monte Carlo; MI=multiple imputation.
[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) with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m).
[b] Number of responders and percentages are based on combined inferential statistics from the MI. Number of responders is calculated as average of numbers of responders from the MI and rounded to integer first, then percentage is calculated using the number of responders divided by the number of subjects analyzed. Similar logic is used for the estimates of number and percentage of non-responders.
[c] The odds ratio was estimated and the p-value was to compare the odds of subjects being a responder in CSF-1 group with the odds in vehicle group based on the primary efficacy analysis.
[d] The risk difference and p-value were estimated by G-computation approach based on the analysis similar to the primary efficacy analysis.
Note: Missing data for the BDCVA (precision vision chart at 40 cm) and BDCVA (ETDRS chart at 4 m) at Visit 3 (Day 8) were imputed using MCMC MI technique prior to obtaining the responses. After the MI, subjects who withdrew due to lack of efficacy or adverse events were set as non-responders.
Source: Reviewer's summary and analyses based on the application.

Based on the collective efficacy evidence from the two adequate and well-controlled trials of NEAR-1 and NEAR-2 studies, Biostatistics concluded that the application provided substantial evidence of efficacy of CSF-1 administered as one drop in each eye bilaterally twice daily, two to three hours apart, in treatment of presbyopia in adults from statistical perspectives.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators in the original NDA submission.

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)

Patient Experience Data

Trials NEAR-1 and NEAR-2
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		Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	See Clinical Efficacy
		☐	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.			

Office of Scientific Investigations (OSI)

From the OSI Clinical Inspections Summary dated August 16, 2023:

Clinical data from Protocols 20-150-0002 (NEAR-1) and 20-150-0003 (NEAR-2) were submitted to the Agency in support of NDA 217836 for the use of Qlosi (pilocarpine hydrochloride ophthalmic solution 0.4%) for the treatment of presbyopia in adults. The clinical investigators, Drs. Debry and Restivo, were inspected in support of this NDA.

Based on the results of these inspections, 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 and were brought to the attention of the review division by email on 8/8/2023. We recommend that the review division conduct sensitivity analyses to determine the impact, if any, on study outcome. On 8/14/23 submission, the applicant responded to the Division's 8/10/23 information request: "The site inspection for Site #41 Dr. Restivo revealed multiple discrepancies between the source documents and eCRF. Please submit an analysis of the primary efficacy endpoint with Dr. Restivo's site excluded."

The applicant's analysis with and without Site #41, demonstrated no significant impact on the primary efficacy analysis.

OPDP and DMEPA

The Office of Prescription Drug Promotion (OPDP) completed a review of the package insert and carton/ container labeling on October 5, 2023.

The Division of Medication Error Prevention and Analysis 1 (DMEPA) completed a review of the originally submitted labeling on June 13, 2023. Revisions were proposed for the draft prescribing information (PI), professional sample and trade container labels and carton labeling.

DMEPA completed a review of the final submitted labeling on October 16, 2023. As currently presented, the dot used to represent the lower-case dotted letter 'i,' was also used to represent the lower case 'l' which may lead to misinterpretation of the proprietary name.

The Applicant did not agree with the Agency recommendation to revise the design, based in part on the following rationale:

• "The proprietary name candidate, Qlosi, underwent rigorous analysis and was compared to potentially similar names that were revealed in a POCA 4.3 search as well as a survey of likely healthcare practitioners that would come in contact with the product. None of the names were found to have significant look-alike or sound-alike similarity with Qlosi. (see NDA 217836, Request For Proprietary Name Review for QLOSI, Module 1.18)."

• "We believe there is minimal risk if there was confusion or misunderstanding 'l' for an 'i'. Qiosi is an odd sequence of letters that does not resemble any ophthalmic brand that could be mistaken or misunderstood by a health care professional within an EMR."

DO agreed with the applicant's rationale for keeping the current design.

DMEPA did not agree with DO's recommendation to utilize the term "single-patient-use vials" in the labeling. DO finds the term acceptable. (b) (4) (label limits use to 3 hours in Section 2 of PI) because there is not enough time for a vial which may have touched the eye to grow sufficient microorganisms to be harmful.

Post-marking Risk Management

There are no proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

Regulatory Action

NDA 217836 Qlosi (pilocarpine ophthalmic solution) 0.4% will be approved for the treatment of presbyopia in adults.

Labeling

Attached is the agreed-upon labeling for NDA 217836 Qlosi (pilocarpine ophthalmic solution) 0.4% for the treatment of presbyopia in adults.

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

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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/

WILLIAM M BOYD
10/17/2023 12:46:55 PM
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WILEY A CHAMBERS
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