CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

Orasis Pharmaceuticals, Ltd (Orasis) submitted a New Drug Application (NDA) for Qlosi (i.e., pilocarpine hydrochloride 0.4% ophthalmic solution, hereinafter referred to as CSF-1). CSF-1 is intended to provide a pharmacologic alternative for the treatment of presbyopia and reduce the use of, and the need for, reading glasses or corrective surgical treatments. Orasis is seeking the approval of CSF-1 for the treatment of presbyopia in adults.

Although the clinical development program consists of one Phase 2b study (18-150-0006) and two pivotal Phase 3 studies (20-150-0002 and 20-150-0003), Orasis explored the Phase 2b study to inform the design of the Phase 3 trials regarding the primary endpoint and investigational drug's dose level. This statistical review assessed the adequacy of the submitted information in these two pivotal studies to support the efficacy of CSF-1.

Study 20-150-0002 (hereinafter referred to as NEAR-1) or 20-150-0003 (hereinafter referred to as NEAR-2) was a 4-visit, Phase 3, randomized, double-masked, vehicle-controlled, parallel-group study evaluating the safety and efficacy of CSF-1 in subjects aged 45-64 years with presbyopia. A total of 309 subjects in NEAR-1 and 304 in NEAR-2 were randomized in a 1:1 ratio to receive either CSF-1 or vehicle twice daily up to 15 days. Randomization was stratified by baseline iris color of study eye (light [blue, hazel, green, and gray] vs. brown) and manifest refraction spherical equivalent (MRSE, -4.5 diopter [D] to < -0.5 D vs. -0.5 D to 0.75 D vs. > 0.75 D to 2.0 D).

In both studies, each enrolled subject was required to complete four scheduled study visits over the study period: screening visit (Visit 1): Days -14 to -1; operative visits (Visits 2-4): Day 1, Day 8, and Day 15. During the three operative visits, study personnel instilled Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments were conducted for two (at Visits 2 and 3) or up to three (at Visit 4) hours following Dose 1. Dose 2 was instilled by study personnel at 10:30 AM ± 30 (at Visits 2 and 3) or 11:30 AM ± 30 (at Visit 4) minutes in each eye. Efficacy and safety assessments were conducted for four (at Visit 2), two (at Visit 3), or five (at Visit 4) hours following Dose 2.

All randomized subjects in NEAR-1 and NEAR-2 were included in the full analysis set (FAS), which was defined as all randomized subjects who received at least one dose of the study drug, to evaluate the efficacy of CSF-1. In both studies, most subjects completed the study. Only 16 (5.2%) subjects in NEAR-1 and 18 (5.9%) subjects in NEAR-2 discontinued the study. A majority of subjects in both studies were female (59.9% in NEAR-1 and 64.1% in NEAR-2), White (75.1% in NEAR-1 and 86.5% in NEAR-2), did not identify as Hispanic or Latino (81.9% in NEAR-1 and 80.9% in NEAR-2), and had brown iris color (54.4% in NEAR-1 and 46.4% in NEAR-2). The average age for subjects in both studies was 54.7 years.

In both studies, treatment efficacy for primary (measured at one hour post Dose 1) and key secondary endpoints (measured at two hours post Dose 1, one hour post Dose 2, and two hours post Dose 2) were assessed at Visit 3 (Day 8). Efficacy assessment was based on the percentage of responders defined as 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 (early treatment of diabetic

retinopathy study [ETDRS] chart at 4 m) in the study eye. To claim a success, CSF-1 should be superior to vehicle for all primary and key secondary endpoints in both NEAR-1 and NEAR-2 studies.

In both studies, data for subjects treated with CSF-1 ophthalmic solution demonstrated efficacy of CSF-1 over vehicle in the primary endpoint and key secondary endpoints. Specifically,

- For the primary endpoint
  - In NEAR-1 study, the percentage of responders in the CSF-1 group (38.7%) was statistically significantly higher than that in the vehicle group (16.9%) at one hour post Dose 1 with (1) adjusted risk difference (ARD): 19.2% (95% confidence interval [CI]: 9.5-28.8), p-value<0.0001; and (2) adjusted odds ratio (AOR) of 2.9 (95% CI:1.7-5.1), p-value=0.0002;
  - In NEAR-2 study, the percentage of responders in the CSF-1 group (41.6%) was statistically significantly higher than that in the vehicle group (21.3%) at one hour post Dose 1 with (1) ARD: 21.9% (95% CI: 11.8-32.0), p-value<0.0001; and (2) AOR: 3.0 (95% CI: 1.8-5.1), p-value<0.0001.
- For the key secondary endpoints (measured at Visit 3 [Day 8] starting two hours post Dose 1 and continued up to two hours post Dose 2)
  - In NEAR-1 study, the percentages of responders in the CSF-1 group were statistically significantly higher as compared to the vehicle group: 39.4% vs. 16.9% at two hours post Dose 1; 47.7% vs. 15.6% at one hour post Dose 2; 38.7% vs. 14.9% at two hours post Dose 2 with the ARDs of 20.3% (95% CI: 10.6-30.1), 29.6% (95% CI: 19.7-39.5), and 21.6% (95% CI: 12.1-31.2), respectively;
  - In NEAR-2 study, the percentages of responders in the CSF-1 group were statistically significantly higher as compared to the vehicle group: 40.3% vs. 20.7% at two hours post Dose 1, 51.9% vs. 16.7% at one hour post Dose 2, 46.1% vs. 19.3% at two hours post Dose 2 with the ARDs of 20.7% (95% CI: 10.6-30.7), 36.2% (95% CI: 26.4-46.1), and 28.4% (95% CI: 18.4-38.3), respectively.

In summary, based on the collective efficacy evidence from the two adequate and well-controlled trials of NEAR-1 and NEAR-2, we conclude 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, as compared to vehicle.

2. INTRODUCTION

2.1 Overview

Orasis submitted this NDA for the use of CSF-1, a pilocarpine hydrochloride 0.4% ophthalmic solution, for the treatment of presbyopia in adults. The clinical development program of CSF-1 consists of one Phase 2b study (18-150-0006) and two pivotal Phase 3 studies (20-150-0002 [NEAR-1] and 20-150-0003 [NEAR-2]). A summary of these studies was outlined in Table 1 below.

Table 1. Summaries of Studies Included in the Efficacy and Safety Analyses

Trial ID	Phase and Design	Treatment Period	Follow-up Period	# Subjects per Arm	Study Population
18-150-0006	Phase 2b multi-center, randomized, double-masked, parallel group factorial trial	15 days	Not applicable	CSF-1 FDC: 53 PH: 55 DS: 58	Healthy adult subjects ages 45 to 64 years who have presbyopia
20-150-0002 (NEAR-1)	Phase 3 multi-center, randomized, double-masked, parallel group vehicle-controlled trial	15 days	Not applicable	CSF-1:155 Vehicle:154	Healthy adult subjects ages 45 to 64 years who have presbyopia
20-150-0003 (NEAR-2)	Phase 3 multi-center, randomized, double-masked, parallel group vehicle-controlled trial	15 days	Not applicable	CSF-1:154 Vehicle:150	Healthy adult subjects ages 45 to 64 years who have presbyopia

Abbreviations: DS=diclofenac sodium, FDC=fixed dose combination, PH=pilocarpine hydrochloride.
Source: Reviewer's summary based on the submission.

The Phase 2b trial was a proof-of-concept trial to inform the study drug's dose level and primary endpoint used in the two pivotal Phase 3 trials. Thus, the focus of this review will be only the two pivotal Phase 3 trials that were designed to evaluate the efficacy and safety of CSF-1 for the treatment of adults with presbyopia.

2.2 Relevant Regulatory Correspondence

Date	Application Number/ Type of Correspondence	Description
4/5/2020	IND131464 Type B Meeting Minutes	During the end-of-Phase-2b meeting, the Agency clarified that in order to be considered a success, a subject should gain ≥3-lines (i.e., halving of visual angle) in best distance corrected near vision acuity at 40 cm AND also not lose ≥5 letters in best distance corrected vision acuity at

		4 m. Also, the Agency agreed that the applicant's strategies to handle missing data/intercurrent events (see Section 3.2.2 for details).
9/21/2021	IND131464 Type C Meeting minutes	FDA had no objection with Orasis's hierarchical testing plan within each branch (i.e., Day 1 or Day 15) once the specific alpha level for testing each branch is specified. As supporting analysis, the Agency did not have objection to the proposed integrated summary of efficacy (ISE) and integrated summary of safety (ISS) plan. The ISE should be placed in Module 2 and the individual clinical study reports with analysis and datasets should be placed in Module 5.
9/7/2022	IND131464 Type B Meeting Minutes	Orasis proposed an ISS and ISE including data from the two Phase 3 pivotal studies of NEAR-1 and NEAR-2. FDA recommended that overall efficacy results and subgroup analyses should be summarized and described separately for all individual studies. FDA agreed that the safety database size is adequate to support the NDA submission under the 505(b)(1) pathway because the applicant utilized results from its own clinical studies consisting of data for 477 subjects treated with CSF-1 for various durations. Also, the entire clinical safety data of Salagen NDA 020237 including 245 patients, treated with oral pilocarpine for one year, will support the requirements for long-term (one year) clinical safety data.

2.3 Data Sources

The primary data sources for this review were the clinical study reports, study protocols, statistical analysis plans, and the analysis and tabulation datasets. These were provided in an electronic submission located at \\CDSESUB1\evsprod\NDA217836\0001. The primary analysis datasets were located at \\CDSESUB1\evsprod\NDA217836\0001\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

We found that the quality of the submitted data and analysis was acceptable.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

The efficacy and safety support for CSF-1 in adult subjects with presbyopia was based on data from two pivotal 4-visit, Phase 3, randomized, double-masked, vehicle-controlled, parallel-group superiority studies of NEAR-1 and NEAR-2.

NEAR-1 and NEAR-2 studies were designed to evaluate the safety and efficacy of CSF-1 compared to vehicle in subjects with presbyopia treated over 15 days. A total of 309 subjects in NEAR-1 and 304 in NEAR-2 were randomized in a 1:1 ratio to receive either CSF-1 or vehicle twice daily. NEAR-1 study was initiated on October 19, 2020, and completed on February 18, 2022, while NEAR-2 study was initiated on October 16, 2020, and completed on February 9, 2022. In both studies, randomization was stratified by baseline iris color of study eye (light [blue, hazel, green, and gray] vs. brown) and manifest refraction spherical equivalent (MRSE, -4.5 diopter [D] to < -0.5 D vs. -0.5 D to 0.75 D vs. > 0.75 D to 2.0 D).

In both studies, each enrolled subject was required to complete four scheduled study visits over the study period: screening visit (Visit 1): Days -14 to -1; operative visits (Visits 2-4): Days 1, 8, and 15. In the screening visit, study personnel instilled one dose of vehicle in each eye for the participants to identify vehicle non-responders who were invited to Visit 2. During the three operative visits, study personnel instilled Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments were conducted for 2 (Visits 2 and 3) or up to 3 (Visit 4) hours post Dose 1. Dose 2 was instilled by study personnel at 10:30 AM ±30 (Visits 2 and 3) or 11:30 AM ±30 (Visit 4) minutes in each eye. Efficacy and safety assessments were conducted for 4 (Visit 2), 2 (Visit 3), or 5 (Visit 4) hours post Dose 2. During the non-operative visits from Days 1 through 15 (i.e., Days 2 to 7 and Days 9 to14), the participants were instructed to instill one drop of assigned treatment bilaterally twice daily: Dose 1 in the morning around 8:30 am and followed by Dose 2 at two hours after Dose 1.

Efficacy Evaluation

All primary and secondary efficacy assessment was based on the percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in BDCVA at 40 cm (precision vision [PV] chart) and no loss in BDCVA ≥ 5 letters (early treatment of diabetic retinopathy study [ETDRS] chart at 4 m) in the study eye. Both treatment efficacy for primary (i.e., one hour post Dose 1) and key secondary (i.e., two hours post Dose 1, one hour post Dose 2, and two hours post Dose 2) endpoints were assessed at Visit 3 (Day 8) for the intent-to-treat participants while the treatment efficacy for other secondary endpoints were assessed at Visit 2 (Day 1: 30 minutes, 1 hour, and 2 hours after Dose 1, 30 minutes, 1 hour, 2, 3, and 4 hours after Dose 2) and Visit 4 (Day 15: 20 minutes, 1 hour, 2, and 3 hours after Dose 1, 20 minutes, 1 hour, 2, 3, 4, and 5 hours after Dose 2).

Other exploratory efficacy endpoints defined in both studies included:

- 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 (PV 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 Visits 2 (Day 1), 3 (Day 8), and 4 (Day 15) in the study eye post Doses 1 and 2;
  - Percentage of subjects with a sustained ≥ 2-line (10-letter) gain from baseline in BDCVA (PV 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 (PV 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 (PV 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 post 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 (PV 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 (PV 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 (PV 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 visual acuity testing conditions:
  - Mean change in pupil diameter under near visual acuity at 40 cm testing conditions, from baseline at each time point at Visits 2 (Day 1), 3 (Day 8), and 4 (Day 15) in the study eye.

All analyses were performed using data from the study eye. To claim a success, the CSF-1 should be superior to the vehicle for all primary and key secondary endpoints in both NEAR-1 and NEAR-2 studies.

3.2.2 Statistical Methodologies

Analysis Sets

- Full Analysis Set (FAS): Defined as all randomized subjects who received at least one 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): Defined as all 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.

Unit of Analysis

The study eye was used for all monocular analyses while the fellow eye was included in all binocular analyses. The study eye was defined by the study investigator as the eye that met all enrollment criteria. If both eyes met all enrollment criteria, then the eye with the worse Visit 2 pre-

treatment/baseline BDCVA at 40 cm (PV chart) was the study eye. If both eyes had the same BDCVA at 40 cm, then the right eye was the study eye.

Handling of Missing Data/Intercurrent Events

Per the submission, Orasis took the following strategies to handle missing data/intercurrent events:

- Discontinuation of study drug and non-optimal compliance was ignored (treatment policy strategy);
- Withdrawal due to lack of efficacy or adverse events (AEs): missing data were singly imputed as failure (hypothetical strategy);
- Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs were imputed to create 25 datasets employing multiple imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methods (hypothetical strategy).
  - The variables of treatment group, baseline for BDCVA at 40 cm and 4 m were included in the MI model.
  - Missing value for the continuous measures (BDCVA at 40 cm and 4 m) were imputed to determine the response variable.
  - Imputation of failure due to lack of efficacy or AEs was assigned after MI was performed.

Reviewer's remark*: The strategy for withdrawal due to lack of efficacy or AEs is actually composite strategy rather than hypothetical strategy stated by Orasis.*

Type I Error Control (Multiplicity Adjustment)

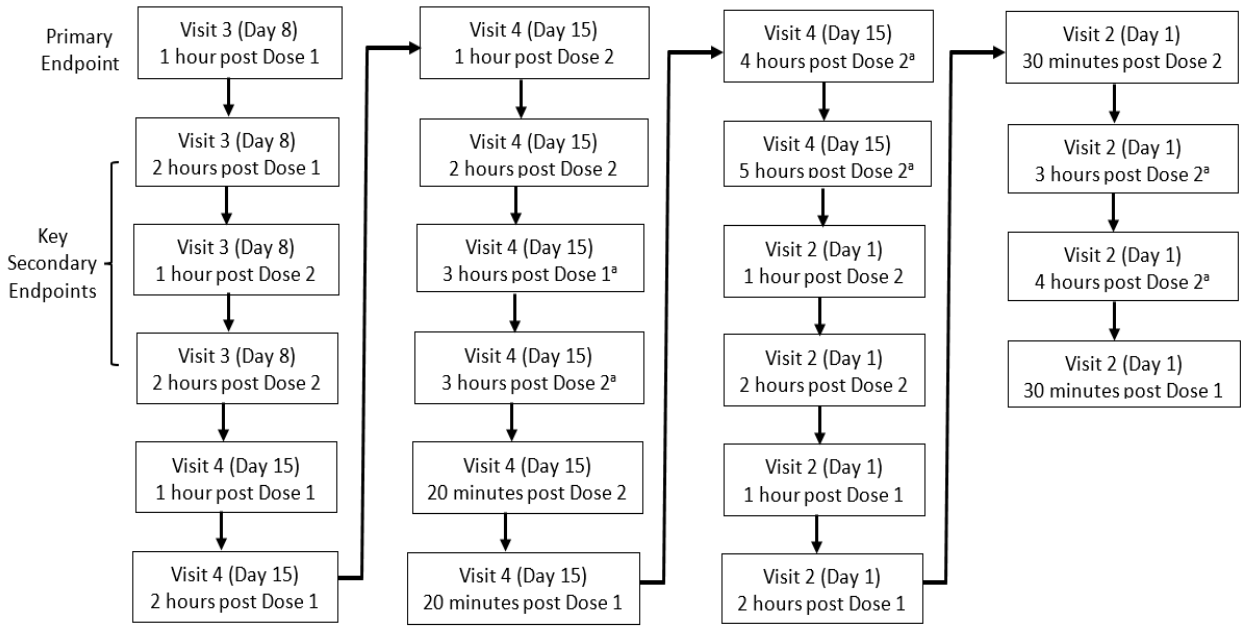
Per the submission, a hierarchical testing strategy was used to adjust the multiplicity for the 22 hypotheses (one for the primary endpoint, three for the key secondary endpoints, and 18 for other secondary endpoints) as follows:

$$H_0: p_{CSF-1} - p_{vehicle} = 0 \text{ vs. } H_a: p_{CSF-1} - p_{vehicle} \neq 0,$$

where p_{CSF-1} and $p_{vehicle}$ were the percentages of study eye with a ≥ 3-line (15-letter) gain from baseline in BDCVA at 40 cm (PV chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) in CSF-1 group and vehicle group, respectively, at the different visit, time point, and post-dose number with the testing order (top to bottom and left to right) as presented in Figure 1.

Specifically, if the primary null hypothesis was rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, then the primary endpoint was considered met and the key secondary efficacy hypotheses were tested. The three key secondary hypotheses were tested in a hierarchical order, each at a 2-sided alpha = 0.05, where inference was made on each null hypothesis only if the prior null hypotheses were rejected in favor of CSF-1. If the primary and key secondary endpoints were met, then the study was considered as a success and the 18 other secondary endpoints (hypotheses) were tested at a two-sided alpha of 0.05 with the hierarchical testing strategy to adjust for multiplicity. If, at any endpoint in the hierarchical testing, statistical significance was not met, there was no need to conduct further analysis of the remaining endpoints.

Figure 1. Fixed Order of Hierarchical Testing for the Primary, Key Secondary, and Other Secondary Endpoints



[a] Indicates time point at which sustained criteria was applied. Sustained time points required the subject to have a response at the indicated time point as well as all earlier time points, back to one hour within the same dose and visit.

Primary Efficacy Analysis

The primary efficacy analysis was conducted in the FAS with missing data handled as discussed in *Handling of Missing Data/Intercurrent Events* subsection.

No eligible subject data were excluded from the FAS due to protocol violations/deviations. MIs of missing values were completed for the continuous measures of BDCVA at 40 cm and 4 m, there from the response variable was determined. Imputation of failure due to lack of efficacy or AEs was assigned after 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 MI model. 25 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. The traditional approach from Rubin (2004)[1] was used to estimate the overall p-value and odds ratio (95% CI).

Orasis conducted four sensitivity analyses for the primary efficacy endpoint as follows:

[1] Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons; 2004 Jun 9.

1. Observed data only using the FAS;
2. All missing data imputed as failure using the FAS;
3. Observed data only using the PPS;
4. Missing data were imputed employing tipping point analysis using the FAS.

The first three sensitivity analyses were performed using a logistic regression model with baseline BDCVA at 40 cm as a covariate and treatment as a main effect. The odds ratio and its 95% CI were provided. P-values were presented for the treatment group using a Wald test. For the last sensitivity analysis, missing values were imputed using tipping point analysis. First, set all records in CSF-1 with missing value as failures and all records in vehicle with missing value as successes; that is the worst case. The imputed data was analyzed using a logistic regression model with baseline BDCVA at 40 cm as a covariate and treatment as a main effect. The p-value, odds ratio, and 95% CI for odds ratio were provided. If the p-value was less than or equal to 0.05 for the worst case, then testing was stopped. If the p-value was greater than 0.05 for the worst case, then the missing records were set as failures or successes in all possible combinations from worse case to the best case until the p-value turned from > 0.05 to ≤ 0.05.

Reviewer's remark: *The p-value stated above from the logistic regression model is basically for comparing the conditional odds of adults becoming responders in the CSF-1 to that in vehicle group. However, the studies' primary and secondary efficacy hypotheses were to test the difference of percentages of responders in CSF-1 and vehicle groups. To test the difference of percentages of responders, we recommend using the G-computation approach[2] [3] from the logistic regression model including continuous covariate(s). The G-computation estimator consistently estimates the population causal risk difference.*

Key Secondary Efficacy Analysis

The key secondary efficacy and its sensitivity analyses were conducted similar to these for the primary efficacy analyses.

Other Secondary Efficacy Analysis

Other secondary efficacy endpoints were analyzed based on the observed data using the same modeling strategy as the primary and key secondary efficacy endpoints. The logistic regression analyses of the other secondary efficacy endpoints were completed using hierarchical testing (see the testing order in Figure 1 for details) to control the overall Type I error. There were no sensitivity analyses conducted for these other secondary endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Subject Disposition

[2] Hernán MA, Robins JM. *Causal Inference*: What If. Boca Raton: Chapman & Hall/CRC, 2020.
[3] Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug information journal: DIJ/Drug Information Association. 2011 July; 45: 481-93.

Table 2 summarized the subject disposition in both studies. As shown, a total of 309 and 304 subjects were enrolled in NEAR-1 and NEAR-2 studies, respectively. In both studies, most subjects completed the studies (293 [94.8%] in NEAR-1 and 286 [94.1%] in NEAR-2). In Near-1 study, the most frequent reason for study discontinuation in the CSF-1 group was withdrawal by subjects (2.6%) and adverse events (2.6%), and in the vehicle group was withdrawal by subjects (1.3%) while in NEAR-2 study the most frequent reason for study discontinuation in the CSF-1 group was withdrawal by subjects (3.9%), and in the vehicle group was lost to follow-up (4.0%). Throughout NEAR-1 study, 16 (5.2%) subjects (CSF-1: 6 [3.9%]; Vehicle: 10 [6.5%]) had at least one major protocol deviation while throughout NEAR-2 Study, 12 (3.9%) subjects (CSF-1: 7 [4.5%]; Vehicle: 5 [3.3%]) had at least one major protocol deviation.

Table 2. Subject Disposition in NEAR-1 and NEAR-2 Studies

	20-150-0002 (NEAR-1)		20-150-0003 (NEAR-2)	
	CSF-1 (N=155)	Vehicle (N=154)	CSF-1 (N=154)	Vehicle (N=150)
	n (%)	n (%)	n (%)	n (%)
Analysis population				
Full analysis set	155 (100)	154 (100)	154 (100)	150 (100)
Per protocol set	149 (96.1)	144 (93.5)	147 (95.5)	145 (96.7)
Safety set	155 (100)	154 (100)	154 (100)	150 (100)
Study completion				
Completed	146 (94.2)	147 (95.5)	144 (93.5)	142 (94.7)
Discontinued	9 (5.8)	7 (4.5)	10 (6.5)	8 (5.3)
Reasons for study discontinuation				
Adverse event	4 (2.6)	1 (0.6)	1 (0.6)	1 (0.7)
Lost to follow-up	0	1 (0.6)	1 (0.6)	6 (4.0)
Physician decision	0	1 (0.6)	0	0
Protocol violation	0	0	1 (0.6)	0
Study terminated by sponsor	0	0	0	0
Withdrawal by subject	4 (2.6)	2 (1.3)	6 (3.9)	1 (0.7)
Death	0	0	0	0
Screen failure	1 (0.6)	2 (1.3)	0	0
Other	0	0	1 (0.6)	0
Subjects with protocol deviation				
Any deviation	100 (64.5)	95 (61.7)	98 (63.6)	86 (57.3)
Major deviation	6 (3.9)	10 (6.5)	7 (4.5)	5 (3.3)
Minor deviation	96 (61.9)	91 (59.1)	98 (63.6)	86 (57.3)

Source: Reviewer's summary based on the study reports.

Demographic and Baseline Characteristics

Table 3 presented a summary of the subjects' demographics and characteristics for the FAS in both studies. Overall, the subject demographics were well-balanced across treatment groups. The average age was 54.7 years in both NEAR-1 and NEAR-2 studies. A majority of subjects were female (NEAR-1: 185 [59.9%]; NEAR-2: 195 [64.1%]), white (NEAR-1: 232 [75.1%]; NRAE-2: 263 [86.5%]), did not identify as Hispanic or Latino (NEAR-1: 253 [81.9%]; NEAR-2: 246 [80.9%]), and had brown eyes (NEAR-1: 168 [54.4%]; NEAR-2: 142 [46.7%]).

Table 3. Summary of Demographic Characteristics

	20-150-0002 (NEAR-1)			20-150-0003 (NEAR-2)		
	CSF-1 (N = 155)	Vehicle (N = 154)	Total (N=309)	CSF-1 (N = 154)	Vehicle (N = 150)	Total (N=305)
Age (Years)						
Mean (SD)	54.8 (4.56)	54.5 (4.88)	54.7 (4.72)	54.6 (4.97)	54.8 (4.81)	54.7 (4.89)
Median (Min, Max)	55.0(45,64)	54.0(45,64)	55.0(45,64)	54.0(45,64)	54.0(45,64)	54.0(45,64)
Sex: n (%)						
Male	62 (40.0)	62 (40.3)	124 (40.1)	53 (34.4)	56 (37.3)	109 (35.9)
Female	93 (60.0)	92 (59.7)	185 (59.9)	101 (65.6)	94 (62.7)	195 (64.1)
Race: n (%)						
AIAN	2 (1.3)	2 (1.3)	4 (1.3)	0 (0)	1 (0.7)	1 (0.3)
Asian	6 (3.9)	14 (9.1)	20 (6.5)	5 (3.2)	7 (4.7)	12 (3.9)
BAA	25 (16.1)	25 (16.2)	50 (16.2)	13 (8.4)	9 (6.0)	22 (7.2)
NHOPI	0 (0)	0 (0)	0 (0)	2 (1.3)	0 (0)	2 (0.7)
White	121 (78.1)	111 (72.1)	232 (75.1)	131 (85.1)	132 (88.0)	263 (86.5)
Multi-Racial	0 (0)	1 (0.6)	1 (0.3)	3 (1.9)	0 (0)	3 (1.0)
Other	1 (0.6)	1 (0.6)	2 (0.6)	0 (0)	1 (0.7)	1 (0.3)
Ethnicity: n (%)						
Hispanic or Latino	33 (21.3)	23 (14.9)	56 (18.1)	30 (19.5)	28 (18.7)	58 (19.1)
Not Hispanic or Latino	122 (78.7)	131 (85.1)	253 (81.9)	124 (80.5)	122 (81.3)	246 (80.9)
Iris color (study eye): n (%)						
Blue	32 (20.6)	39 (25.3)	71 (23.0)	34 (22.1)	49 (32.7)	83 (27.3)
Brown	83 (53.5)	85 (55.2)	168 (54.4)	71 (46.1)	70 (46.7)	141 (46.4)
Hazel	29 (18.7)	19 (12.3)	48 (15.5)	34 (22.1)	17 (11.3)	51 (16.8)
Green	9 (5.8)	11 (7.1)	20 (6.5)	13 (8.4)	11 (7.3)	24 (7.9)
Gray	2 (1.3)	0 (0)	2 (0.6)	2 (1.3)	3 (2.0)	5 (1.6)
RSF: iris color n (%)						
Light	71 (45.8)	70 (45.5)	141 (45.6)	82 (53.2)	80 (53.3)	162 (53.3)
Brown	84 (54.2)	84 (54.5)	168 (54.4)	72 (46.8)	70 (46.7)	142 (46.7)
RSF: MRSE, n (%)						
-4.5 D to < -0.5 D	35 (22.6)	32 (20.8)	67 (21.7)	31 (20.1)	30 (20.0)	61 (20.1)
-0.5 D to ≤ 0.75 D	88 (56.8)	90 (58.4)	178 (57.6)	91 (59.1)	89 (59.3)	180 (59.2)
>0.75 D to 2.0 D	32 (20.6)	32 (20.8)	64 (20.7)	32 (20.8)	31 (20.7)	63 (20.7)

Abbreviations: AIAN=American Indian or Alaska Native; BAA= American Indian or Alaska Native; D=diopter; eCRF=electronic case report form; FAS=full analysis set; MRSE=manifest refraction spherical equivalent; NHOPI=Native Hawaiian or Other Pacific Islander; SD=standard deviation; RSF=randomized by stratification factor.

Note: N is number of subjects from FAS in that treatment arm and the denominator for percentages. n is number of subjects with a non-missing value. Light iris color includes blue, hazel, green, and gray iris. Multi-racial is marked if a subject records more than one race, including other, on their eCRF.

Source: Reviewer's summary based on the application.

3.2.4 Efficacy Results

In this section, the results for the primary and secondary (key and other secondary) efficacy variables in both studies are presented and discussed.

Efficacy Results for the Primary Endpoint

Table 4 summarized the results for the primary endpoint (measured at Visit 3 [Day 8] one hour post Dose 1 on FAS) in both studies that were also presented in Figure 2. As shown, subjects randomized to the CSF-1 group had approximate three (NEAR-1: 2.9 [95% CI: 1.7-5.1]; NEAR-2: 3.0 [95% CI: 1.8-5.1]) times the odds of a ≥ 3-line (15- letters) improvement in monocular BDCVA at 40 cm and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) compared to subjects randomized to the vehicle group. Orasis stated that at Visit 3 (Day 8) one hour post Dose 1, a statistically significantly 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 (NEAR-1: 60 [38.7%] and p-value = 0.0002; NEAR-2: 64 [41.6%] and p-value < 0.0001) and vehicle groups (NEAR-1: 26 [16.9%]; NEAR-2: 32 [21.3%]).

The results for the sensitivity analyses described in Section 3.2.2 were shown in the Appendix (Table 10 through Table 13). In general, the findings from the sensitivity analysis were consistent with these from the primary analysis except for minor numerical differences.

Reviewer's remark: *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 (see the results in Table 4 for details). We recommend 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.*

Table 4. 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.

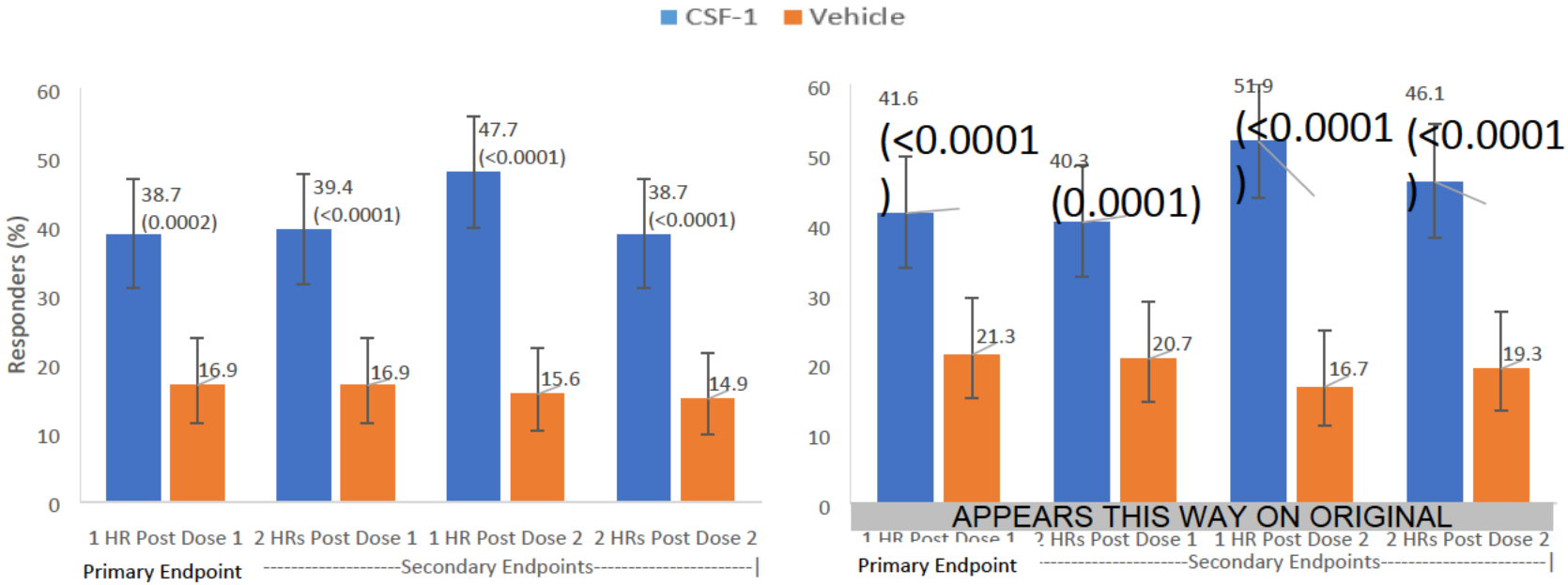
[c] The odds ratio was estimated and the p-value was to compare the odds of subjects being a responder in CSF-1 group with the odds in vehicle group based on the primary efficacy analysis.

[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.

Figure 2. 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)-Percentage (95% CI) of Responders[1] and P-value[2] for the Comparison between CSF-1 and Vehicle--FAS MCMC Multiple Imputation in NEAR-1 and NEAR-2 Studies (Left: NEAR-1; Right: NEAR-2)



Abbreviations: BDCVA = best distance corrected visual acuity; CI=confidence interval; ETDRS = early treatment of diabetic retinopathy study; HR=hour; MCMC = Markov Chain Monte Carlo.

[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) with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m). Number of responders and percentages are based on combined inferential statistics from the multiple imputation. Number of responders is calculated as average of numbers of responders from the multiple imputation and rounded to integer first, then percentage is calculated using the number of responders divided by the number of subjects analyzed. The two-sided 95% CIs are based on Clopper Pearson method.

[2]At each time point and for each imputed dataset (in total 25), Orasis fitted a logistic regression model including dependent variable of responder (yes and no) and independent variable of treatment group (CSF-1 and vehicle) and baseline BDCVA (at 40 cm). The p-value is to compare the odds of subjects being a responder in CSF-1 group with that in vehicle group based on the primary and key secondary efficacy analyses. Using the similar technique, we used the G-computation approach to estimate the p-values for comparing the difference of the percentages of responders in CSF-1 and vehicle groups. There were only two different p-values for one hour post Dose 1 in NEAR-1 study and two hours post Dose 1 in NEAR-2 study and both p-values<0.0001.

Efficacy Results for the Key Secondary Endpoints

All results were summarized in Table 5 and presented in Figure 2 for both studies. Orasis stated that "*All treatment comparisons for the key secondary endpoints were done with logistic regression. However, to assist the clinical interpretation, results are expressed in terms of percentages of responders in each treatment group with the treatment effect p-value from the logistic regression model*." As shown, at Visit 3 and all time points assessed, subjects randomized to the CSF-1 group had significantly higher odds (NEAR-1: 3.0 [95% CI: 1.7-5.3] for two hours post Dose 1, 4.8 [95% CI: 2.7-8.4] for one hour post Dose 2, 3.4 [95% CI: 1.9-6.1] for two hours post Dose 2; NEAR-2: 2.8 [95% CI: 1.7-4.8] for two hours post Dose 1, 6.0 [95% CI: 3.4-10.5] for one hour post Dose 2, 4.2 [95% CI: 2.4-7.2] for two hours post Dose 2) 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) than subjects in the vehicle group. Also, in both study a significantly greater percentage of subjects in the CSF-1 group had a ≥ 3-line (15-letters) improvement in monocular BDCVA at 40 cm with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) compared to vehicle:

- NEAR-1 study
  - 39.4 vs. 16.9 (adjusted risk difference [ARD]: 20.3 [95% CI: 10.6-30.1]; p-value<0.0001) for two hours post Dose 1,
  - 47.7 vs. 15.6 (ARD: 29.6 [95% CI: 19.7-39.5]; p-value<0.0001) for one hour post Dose 2,
  - 38.7 vs. 14.9 (ARD: 21.6 [95% CI: 12.1-31.2]; p-value<0.0001) for two hours post Dose 2;
- NEAR-2 study
  - 40.3 vs. 20.7 (ARD: 20.7 [95% CI: 10.6-30.7]; p-value<0.0001) for two hours post Dose 1,
  - 51.9 vs. 16.7 (ARD: 36.2 [95% CI: 26.4-46.1]; p-value<0.0001) for one hour post Dose 2,
  - 46.1 vs. 19.3 (ARD: 28.4 [95% CI:18.4-38.3]; p-value<0.0001) for two hours post Dose 2.

The results for the key secondary endpoint sensitivity analyses described in Section 3.2.2 were shown in the Appendix (Table 14 through Table 17). In general, the findings from the sensitivity analysis were consistent with these from the primary analysis above except for minor numerical differences.

Reviewer's remark: *Orasis estimated the conditional odds ratio (95% CI) and used the p-value for comparing the conditional odds of subjects being a responder in CSF-1 group with that in vehicle group to compare 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 (95% CIs) and p-values for testing risk differences (see the results in Table 5 for details). We recommend using these risk differences (95% CIs) and p-values estimated by G-computation approach to interpret the percentages of responders in the CSF-1 and vehicle groups. As shown, there were only two different p-values for one hour post Dose 1 in NEAR-1 study and two hours post Dose 1 in NEAR-2 study and both p-values<0.0001.*

Table 5. Visit 3 (Day 8): Key Secondary 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), FAS (MCMC MI)

Parameter statistics	20-150-0002 (NEAR-1) CSF-1 (N=155)	20-150-0002 (NEAR-1) Vehicle (N=154)	20-150-0003 (NEAR-2) CSF-1 (N=154)	20-150-0003 (NEAR-2) Vehicle (N=150)
2-Hour Post Dose 1				
Number (%) of responders [a b]	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)
Comparisons (CSF-1 vs. vehicle)				
Adjusted odds ratio (95% CI) [c]	3.0 (1.7, 5.3)		2.8 (1.7, 4.8)	
p-value [c]	<0.0001		0.0001	
Adjusted risk difference (%, 95% CI) [d]	20.3 (10.6, 30.1)		20.7 (10.6, 30.7)	
p-value [d]	<0.0001		<0.0001	
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)
Comparisons (CSF-1 vs. vehicle)				
Adjusted odds ratio (95% CI) [c]	4.8 (2.7, 8.4)		6.0 (3.4,10.5)	
p-value [c]	<0.0001		<0.0001	
Adjusted risk difference (%, 95% CI) [d]	29.6 (19.7, 39.5)		36.2 (26.4, 46.1)	
p-value [d]	<0.0001		<0.0001	
2-Hour 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)
Comparisons (CSF-1 vs. vehicle)				
Adjusted odds ratio (95% CI) [c]	3.4 (1.9, 6.1)		4.2 (2.4, 7.2)	
p-value [c]	<0.0001		<0.0001	
Adjusted risk difference (%, 95% CI) [d]	21.6 (12.1, 31.2)		28.4 (18.4, 38.3)	
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 key secondary efficacy analysis.
[d] The risk difference and p-value were estimated by G-computation approach based on the analysis similar to the key secondary 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) are imputed using MCMC MI technique prior to obtaining the responses. After the MI, subjects who withdrew due to lack of efficacy or adverse events are set as non-responders.

Source: Reviewer's summary and analyses based on the application.

Efficacy Results for Other Secondary Endpoints

The results for other secondary endpoints were summarized in Table 6 and presented in Figure 3 and Figure 4. The hierarchical testing with p-values for the comparisons of the percentages of responders in the CSF-1 and vehicle groups were presented in Figure 5 while the p-values were for comparing the odds in both groups were presented in Figure 6. As shown, these p-values implied the same inference and were with minor numerical differences.

As shown, for NEAR-1 Study:

- At all-time points and visits assessed, a statistically significantly (i.e., p-value < 0.05) greater percentage of subjects in the CSF-1 group were responders compared to the vehicle group.
- The statistically significantly greater percentage of responders was noted in the CSF-1 as early as 30 minutes after the initial treatment on Day 1.
- Day 15 results showed that this statistically significant effect was maintained throughout the day over the eight hours of observation. Additionally, at Day 15 (eight hours post Dose 1), three times more CSF-1 treated subjects were counted as responders compared to vehicle group.

As shown, for NEAR-2 Study:

- Taking the hierarchal testing into account, at Visit 4 (Day 15), one hour post Dose 1, two hours post Dose 1, one hour post Dose 2, two hours post Dose 2, three hours post Dose 1 (sustained), three hours post Dose 2 (sustained), 20 minutes post Dose 2, 20 minutes post Dose 1, and four hours post Dose 2 (sustained), a significantly greater percentage of subjects in the CSF-1 group were responders compared to vehicle group. The difference between CSF-1 and vehicle was not statistically significant ($p<0.05$) at Visit 4 (Day 15) five hours post Dose 2 (eight hours post Dose 1) and at Visit 2 (Day 1) four hours post dose 2 (six hours post Dose 1), but a numerically higher percentage of CSF-1 treated subjects displayed a trend similar to other time points (Figure 3 and Figure 4).
- Due to the hierarchical multiplicity adjustment, not all visits and time points had statistically significant differences in the number of responders in the CSF-1 group compared to the vehicle group. However, when assessing the results chronologically, a consistent effect, similar to the effect at Visit 3 (Day 8) and Visit 4 (Day 15), was observed across all remaining time points at Visit 2 (Day 1).
- Overall, the observed percentages of responders were consistently higher in CSF-1 treated subjects at any time point at Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15) compared to vehicle group. Furthermore, there was an apparent increase of the effect size observed in the CSF-1 group, between Day 1, Day 8, and Day 15.

3.2.5 Efficacy Conclusions

Based on the collective efficacy evidence from the two adequate and well-controlled NEAR-1 and NEAR-2 studies, we conclude that the CSF-1 provided substantial evidence of the 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. The results from the sensitivity analyses supported these findings except for minor numerical differences.

Table 6. Visit 2 (Day 1) and Visit 4 (Day 15): Other Secondary Efficacy Analysis of Study Eyes 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**)** in NEAR-1 and NEAR-2 Studies

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)
	VISIT 2 (DAY 1)			
30 minutes post-dose 1				
Number (%) of responders [a b]	29 (18.7)	3 (2.0)	23 (14.9)	10 (6.7)
Number (%) of non-responders	126 (81.3)	150 (98.0)	131 (85.1)	140 (93.3)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	11.1 (3.3, 38.0)		2.6 (1.2, 5.6)	
p-value	<0.0001		0.0185	
1-hour post-dose 1				
Number (%) of responders	38 (24.5)	8 (5.2)	34 (22.1)	13 (8.7)
Number (%) of non-responders	117 (75.5)	146 (94.8)	120 (77.9)	137 (91.3)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	5.8 (2.6, 13.3)		3.2 (1.6, 6.3)	
p-value	<0.0001		0.0011	
2-hour post-dose 1				
Number (%) of responders	37 (23.9)	8 (5.2)	32 (20.8)	17 (11.3)
Number (%) of non-responders	118 (76.1)	145 (94.8)	122 (79.2)	133 (88.7)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	5.6 (2.4, 12.8)		2.1 (1.1, 4.0)	
p-value	<0.0001		0.0235	
30 minutes post-dose 2				
Number (%) of responders a b	61 (39.6)	22 (14.4)	44 (28.6)	25 (16.7)
Number (%) of non-responders	93 (60.4)	131 (85.6)	110 (71.4)	125 (83.3)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.8 (2.1, 6.6)		2.3 (1.3, 4.0)	
p-value	<0.0001		0.0054	
1-hour post-dose 2				
Number (%) of responders	66 (42.9)	20 (13.1)	47 (30.5)	23 (15.3)
Number (%) of non-responders	88 (57.1)	133 (86.9)	107 (69.5)	127 (84.7)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	4.9 (2.7, 8.7)		2.7 (1.5, 4.7)	
p-value	<0.0001		0.0008	
2-hour post-dose 2				
Number (%) of responders	51 (33.1)	21 (13.7)	47 (30.5)	22 (14.7)
Number (%) of non-responders	103 (66.9)	132 (86.3)	107 (69.5)	128 (85.3)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.0 (1.7, 5.4)		2.7 (1.5, 4.9)	
p-value	0.0003		0.0007	

3-hour post-dose 2, sustained				
Number (%) of responders	31 (20.1)	9 (5.9)	23 (14.9)	10 (6.7)
Number (%) of non-responders	123 (79.9)	144 (94.1)	131 (85.1)	139 (93.3)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.8 (1.7, 8.4)		2.6 (1.2, 5.7)	
p-value	0.0010		0.0183	
4-hour post-dose 2, sustained				
Number (%) of responders	24 (15.6)	8 (5.2)	14 (9.1)	9 (6.0)
Number (%) of non-responders	130 (84.4)	145 (94.8)	140 (90.9)	140 (94.0)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.1 (1.4, 7.3)		1.6 (0.7, 3.9)	
p-value	0.0075		0.2850	
VISIT 4 (DAY 15)				
20 minutes post-dose 1				
Number (%) of responders	45 (30.8)	26 (17.7)	51 (35.4)	29 (20.6)
Number (%) of non-responders	101 (69.2)	121 (82.3)	93 (64.6)	112 (79.4)
Comparisons (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	1.9 (1.1, 3.4)		2.3 (1.3, 4.1)	
p-value	0.0194		0.0025	
1-hour post-dose 1				
Number (%) of responders	68 (46.6)	33 (22.4)	71 (49.3)	44 (31.2)
Number (%) of non-responders	78 (53.4)	114 (77.6)	73 (50.7)	97 (68.8)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	2.9 (1.7, 4.8)		2.2 (1.4, 3.6)	
p-value	<0.0001		0.0015	
2 hours post-dose 1				
Number (%) of responders	69 (47.3)	31 (21.1)	71 (49.3)	36 (25.5)
Number (%) of non-responders	77 (52.7)	116 (78.9)	73 (50.7)	105 (74.5)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.2 (1.9, 5.4)		3.0 (1.8, 5.0)	
p-value	<0.0001		<0.0001	
3 hours post-dose 1, sustained				
Number (%) of responders	46 (31.5)	18 (12.2)	44 (30.6)	24 (16.9)
Number (%) of non-responders	100 (68.5)	129 (87.8)	100 (69.4)	118 (83.1)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.1 (1.7, 5.8)		2.3 (1.3, 4.1)	
p-value	0.0003		0.0047	
20 minutes post-dose 2				
Number (%) of responders	69 (47.3)	37 (25.2)	66 (45.8)	34 (23.9)
Number (%) of non-responders	77 (52.7)	110 (74.8)	78 (54.2)	108 (76.1)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	2.5 (1.5, 4.2)		2.9 (1.7, 4.9)	
p-value	0.0003		<0.0001	

1-hour post-dose 2				
Number (%) of responders	75 (51.4)	37 (25.2)	84 (58.3)	31 (21.8)
Number (%) of non-responders	71 (48.6)	110 (74.8)	60 (41.7)	111 (78.2)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.0 (1.8, 5.0)		5.5 (3.2, 9.3)	
p-value	<0.0001		<0.0001	
2 hours post-dose 2				
Number (%) of responders	69 (47.3)	23 (15.6)	68 (47.2)	30 (21.1)
Number (%) of non-responders	77 (52.7)	124 (84.4)	76 (52.8)	112 (78.9)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	4.7 (2.7, 8.2)		3.5 (2.1, 5.9)	
p-value	<0.0001		<0.0001	
3 hours post-dose 2				
Number (%) of responders	45 (30.8)	12 (8.2)	40 (27.8)	20 (14.1)
Number (%) of non-responders	101 (69.2)	135 (91.8)	104 (72.2)	122 (85.9)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	4.8 (2.4, 9.6)		2.5 (1.4, 4.6)	
p-value	<0.0001		0.0032	
4 hours post-dose 2, sustained				
Number (%) of responders	37 (25.3)	12 (8.2)	32 (22.2)	19 (13.5)
Number (%) of non-responders	109 (74.7)	135 (91.8)	112 (77.8)	122 (86.5)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.6 (1.8, 7.3)		2.0 (1.0, 3.7)	
p-value	0.0004		0.0389	
5 hours post-dose 2, sustained				
Number (%) of responders	30 (20.5)	10 (6.8)	27 (18.8)	17 (12.1)
Number (%) of non-responders	116 (79.5)	137 (93.2)	117 (81.3)	124 (87.9)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI)	3.3 (1.5, 7.2)		1.8 (0.9, 3.5)	
p-value	0.0021		0.0892	

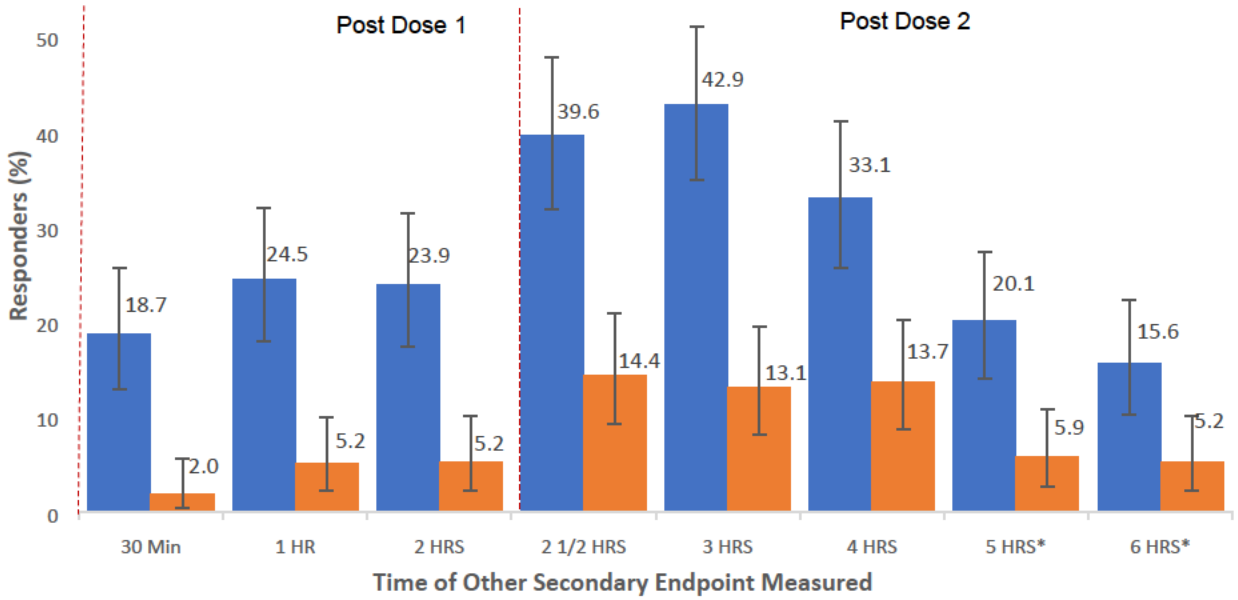
Abbreviations: BDCVA = Best Distance-Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment of Diabetic Retinopathy Study.

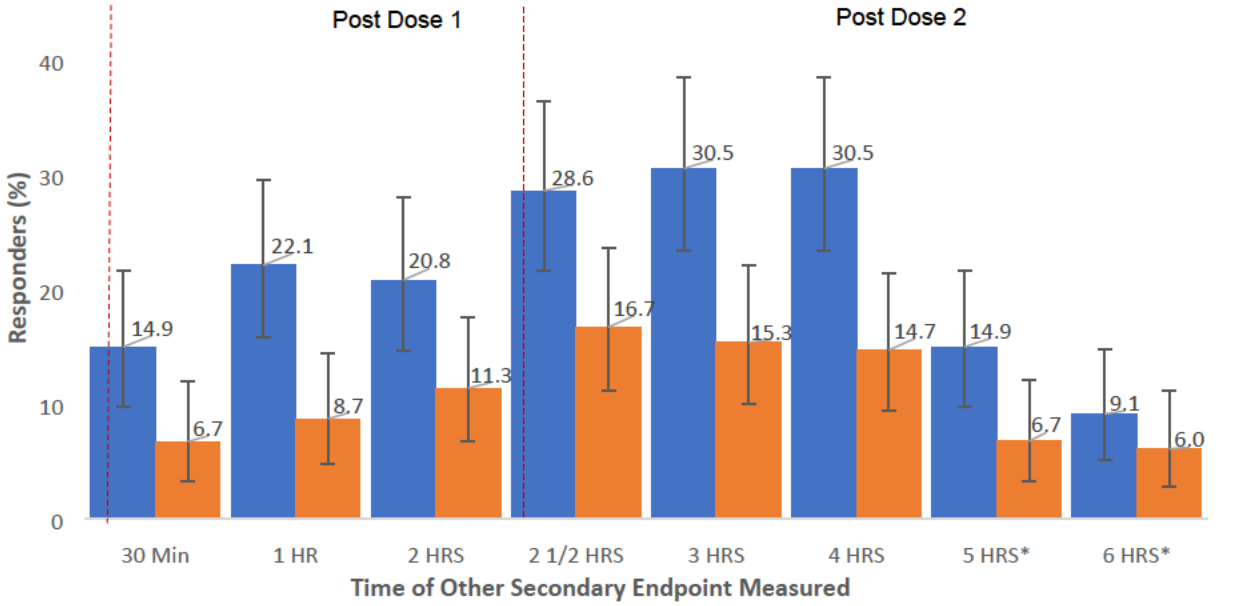
[a] Responder is defined as a subject whose study eye achieves a ≥ 3-line (15-letter) gain from baseline in BDCVA (PV chart at 40 cm) with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m).

[b] Number of responders and percentages are based on combined inferential statistics from the multiple imputation. Number of responders is calculated as average of numbers of responders from the multiple imputation 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.

Note: A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

Figure 3. 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)- Percentage (95% CI) of Responders[1] in CSF-1 and Vehicle - FAS Observed Data Only in NEAR-1 and -2 Studies (Top: NEAR-1; Bottom: NEAR-2)

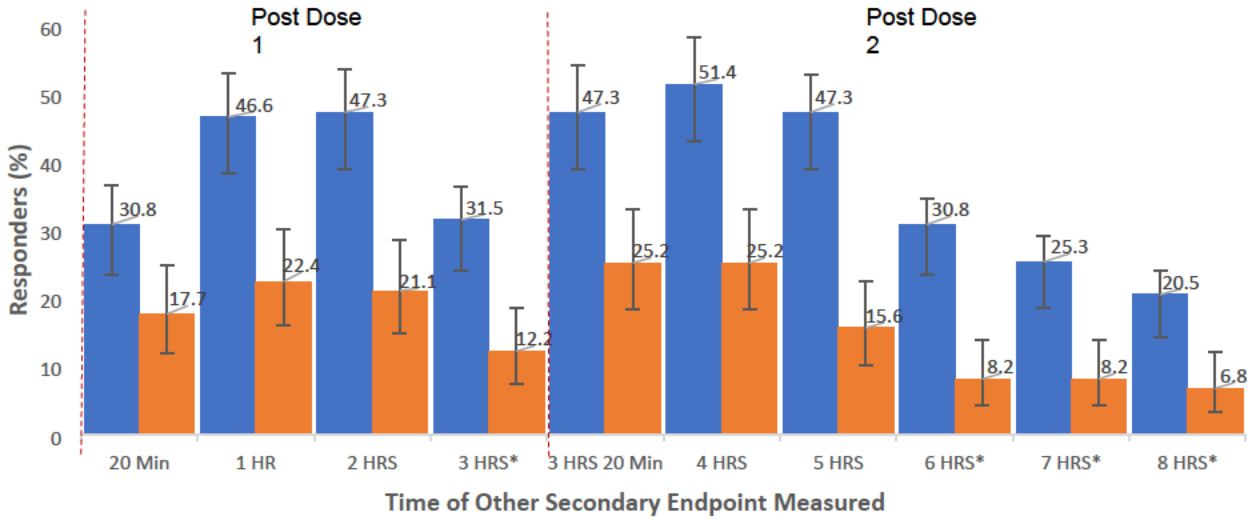


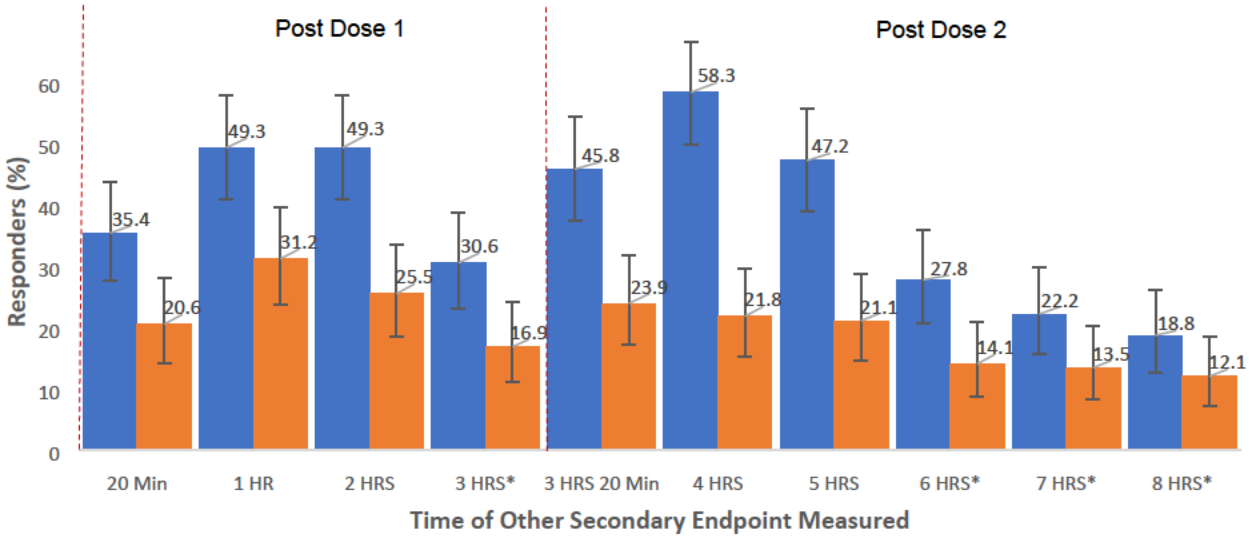


Abbreviations: BDCVA = best distance corrected visual acuity; CI=confidence interval; ETDRS = early treatment of diabetic retinopathy study; HR=hour, Min=minutes.

[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) with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m). Denominators of percentages are the number of subjects without missing data at each time point. The two-sided 95% CIs are based on Clopper Pearson method.

Figure 4. 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) - Percentage (95% CI) of Responders[1] in CSF-1 and Vehicle - FAS Observed Data Only in NEAR-1 and -2 Studies (Top: NEAR-1; Bottom: NEAR-2)

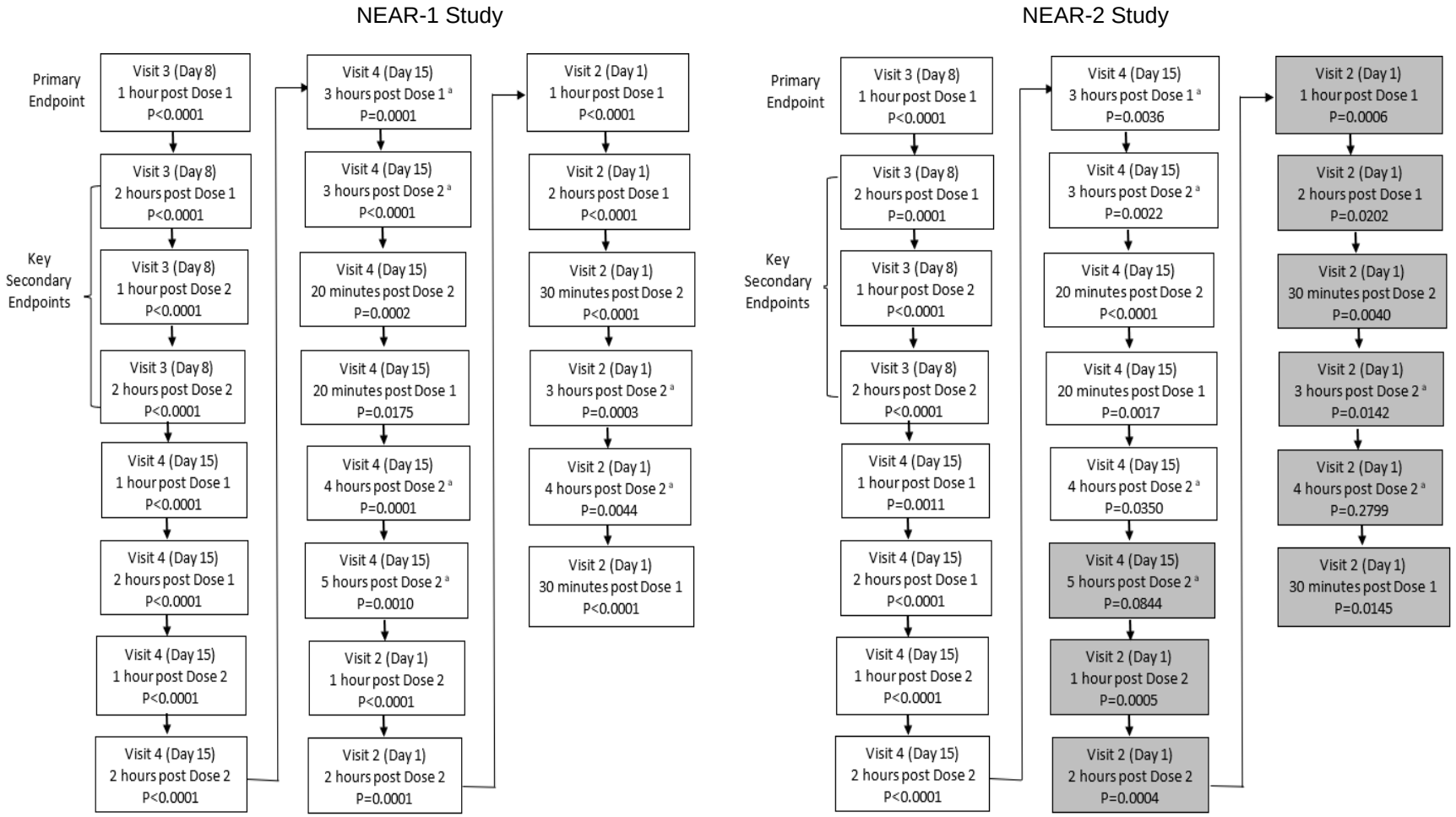




Abbreviations: BDCVA = best distance corrected visual acuity; CI=confidence interval; ETDRS = early treatment of diabetic retinopathy study; HR=hour, Min=minutes.

[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) with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m). Denominators of percentages are the number of subjects without missing data at each time point. The two-sided 95% CIs are based on Clopper Pearson method.

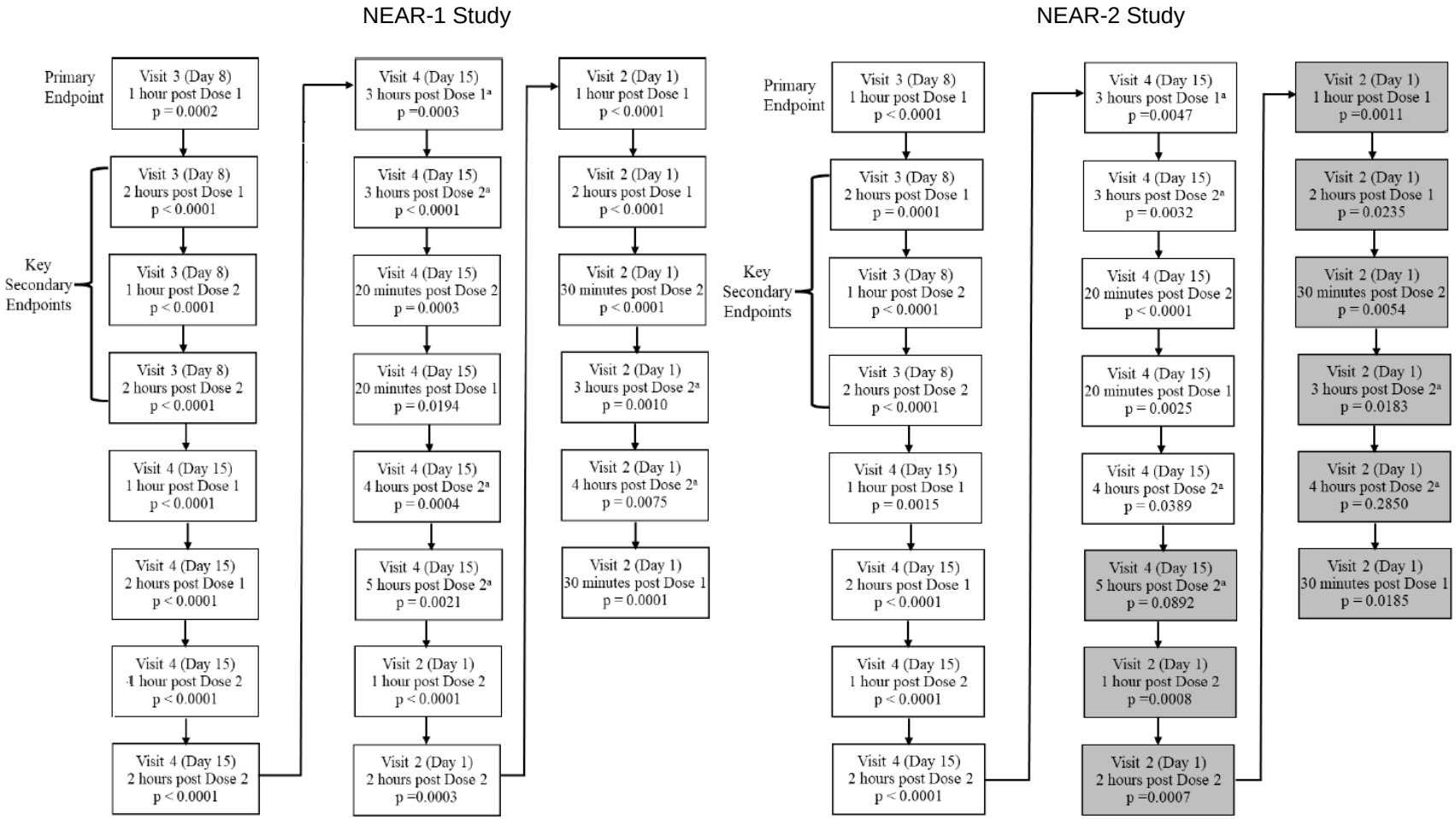
Figure 5. Hierarchical Results of Primary, Key Secondary, and Other Secondary Endpoints: Percentage of Subjects with a ≥ 3-line (15-letter) Gain, from Baseline, in BDCVA at 40 cm (Precision Vision Chart) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) by Reviewer



[a] Indicates time points at which sustained criteria was applied. Sustained time points required the subject to have a response at the indicated time point as well as all earlier time points, back to one hour within the same dose and visit.

Note: Gray shaded boxes indicate time points where statistical significance was not met within hierarchal testing. Orasis fitted a logistic regression model including dependent variable of responder (yes/no) and independent variable of treatment group and baseline BDCVA (at 40 cm). With the same model, we used G-computation approach to estimate the p-values for comparing the percentages of responders in CSF-1 and vehicle groups.

Figure 6. Hierarchical Results of Primary, Key Secondary, and Other Secondary Endpoints: Percentage of Subjects with a ≥ 3-line (15-letter) Gain, from Baseline, in BDCVA at 40 cm (Precision Vision Chart) and No Loss in BDCVA ≥ 5 Letters (ETDRS Chart at 4 m) by Orasis



[a] Indicates time points at which sustained criteria was applied. Sustained time points required the subject to have a response at the indicated time point as well as all earlier time points, back to one hour within the same dose and visit.

Note: Gray shaded boxes indicate time points where statistical significance was not met within hierarchal testing.

Orasis fitted a logistic regression model including dependent variable of responder (yes/no) and independent variable of treatment group and baseline BDCVA (at 40 cm). The p-values for comparing the odds of subjects were responders in CSF-1 and vehicle groups.

3.3 Evaluation of Safety

In this section, we provided and discussed a high-level summary of the safety data. For a comprehensive safety evaluation, we deferred to the FDA medical review.

Analysis Set

Safety analysis set (SAF) was defined as all subjects who received at least one dose of the study drug.

Unit of Analysis

Both eyes were displayed and analyzed for all ophthalmic safety variables.

Safety Analysis

All safety analyses were conducted using the SAF data. All AEs collected in the eCRFs were presented in data listings, but only treatment-emergent adverse events (TEAEs) were summarized in data tables. An overall summary was presented that included the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment group. If a subject reported more than one TEAE, the TEAE was only counted once at the maximal severity.

Summary of Treatment-Emergent Adverse Events

Table 7 summarized the adverse events for both NEAR-1 and NEAR-2 studies. As shown, TEAEs were summarized separately for ocular and non-ocular events on the safety population (NEAR-1: n = 309; NEAR-2: n=304). The total number of TEAEs reported was 57 in NEAR-1 and 123 in NEAR-2. A total of 39 (12.6%) subjects (26 [16.8%] in CSF-1 and 13 [8.4%] in vehicle) had at least one TEAE in NEAR-1 study while a total of 81 (26.6%) subjects (59 [38.6%] in CSF-1 and 22 [14.6%] in vehicle) had at least one TEAE in NEAR-2 study.

In NEAR-1, mild ocular TEAEs were reported in 6.8% of all subjects, and out of the 23 subjects reporting ocular TEAEs, 21 (91.3%) subjects reported mild as their most severe event while in NEAR-2 mild ocular TEAEs were reported in 19.4% of all subjects, and out of the 61 subjects reporting ocular TEAEs, 59 (96.7%) subjects reported mild as their most severe event. Moderate ocular TEAEs were reported in two subjects (0.6%, both in CSF-1 group in NEAR-1; 0.7%, both in CSF-1 in NEAR-2). One subject (0.3% in CSF-1 group) and a total of eight (2.6%) subjects (3 [2.0%] in CSF-1 and 5 [3.3%] in vehicle) reported moderate non-ocular TEAEs in NEAR-1 and NEAR-2, respectively. No severe ocular TEAEs were reported in both studies, and two severe (0.6%; both in vehicle group) non-ocular TEAEs were reported in NEAR-1 and no non-ocular TEAEs were reported in NEAR-2.

One subject (0.6% in NEAR-1 and 0.7% in NEAR-2) in the vehicle group reported one non-ocular SAE. In both studies, no ocular SAEs were reported in either treatment group. A total of three (1.9%) subjects (all 3 in the CSF-1) and two (0.7%) subjects (1 [0.7%] in CSF-1 and 1

[0.7%] in vehicle) reported an ocular TEAE leading to study discontinuation in NEAR-1 and NEAR-2, respectively. A total of four subjects (3 [1.9%] in CSF-1; 1 [0.6%] in vehicle) and two subjects (1 [0.7%] in CSF-1; 1 [0.7%] in vehicle) reported a non-ocular TEAE leading to study discontinuation in NEAR-1 and NEAR-2, respectively. There were no ocular or non-ocular TEAEs leading to death in both studies.

Table 7. Overall Summary of Adverse Events (Safety Analysis Set)

	NEAR-1			NEAR-2		
	CSF-1 (N = 155) n (%)	**Vehicle (N = 154) n (%)**	**Total (N = 309) n (%)**	**CSF-1 (N = 154) n (%)**	**Vehicle (N =150) n (%)**	**Total (N =304) n (%)**
Number of TEAEs	37	20	57	86	37	123
Number of subjects with ≥1 TEAE	26 (16.8)	13 (8.4)	39 (12.6)	59 (38.6)	22 (14.6)	81 (22.6)
Number of Ocular TEAEs	19	8	27	56	24	80
Number of subjects with ≥1 ocular TEAE	17 (11.0)	6 (3.9)	23 (7.4)	43 (28.1)	18 (11.9)	61 (20.1)
Number of non-ocular TEAEs	18	12	30	30	13	43
Number of subjects with ≥1 non-ocular TEAE	13 (8.4)	8 (5.2)	21 (6.8)	26 (17.0)	9 (6.0)	35 (11.5)
Number of ocular SAEs	0	0	0	0	0	0
Number of subjects with ≥1 ocular SAE	0	0	0	0	0	0
Number of non-ocular SAEs	0	1	1	0	1	1
Number of subjects with ≥1 non-ocular SAE	0	1 (0.6)	1 (0.3)	0	1 (0.7)	1 (0.7)
Number of ocular TEAEs LTSD	3	0	3	1	1	2
Number of subjects with ocular TEAEs LTSD	3 (1.9)	0	3 (1.0)	1 (0.7)	1 (0.7)	2 (0.7)
Number of non-ocular TEAEs LTSD	6	1	7	1	1	2
NOS with non-ocular TEAEs LTSD	3 (1.9)	1 (0.6)	4 (1.3)	1 (0.7)	1 (0.7)	2 (0.7)
NOS with ocular TEAEs by maximum severity[a]						
Mild	15 (9.7)	6 (3.9)	21(6.8)	41 (26.8)	18 (11.9)	59 (19.4)
Moderate	2 (1.3)	0	2 (0.6)	2 (1.3)	0	2(0.7)
Severe	0	0	0	0	0	0
NOS with non-ocular TEAEs by maximum severity[a]						
Mild	12 (7.7)	6 (3.9)	18 (5.8)	23 (15.0)	4 (2.6)	27 (8.9)
Moderate	1 (0.6)	0	1 (0.3)	3 (2.0)	5 (3.3)	8 (2.6)
Severe	0	2 (1.3)	2 (0.6)	0	0	0
NOS with ocular TEAEs leading to death	0	0	0	0	0	0
NOS with non-ocular TEAEs leading to death	0	0	0	0	0	0

Abbreviations: AE = adverse event; N = subjects in the treatment arm; NOS=number of subjects; LTSD=leading to study discontinuation; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] If subjects experienced multiple TEAEs, subjects were counted only once for the maximum severity that occurred.
Note: N was used as the denominator in the calculation of percentages; A TEAE is defined as an AE that occurred or worsened after the first dose of investigational product.

In both studies, there were no safety concerns observed in the CSF-1 treatment group and no ocular SAEs were reported. In both studies, one non-ocular SAE was reported in the vehicle group during the study (enteritis in NEAR-1 and arthritis infective in NEAR-2) and assessed as not related to

the study drug. The TEAEs reported in both studies were primarily of mild intensity: two subjects reporting an ocular TEAE of moderate severity and no subjects reporting any severe ocular TEAE in both studies. Three (1.0%) in NEAR-1 and two (0.7%) in NEAR-2 subjects reported an ocular TEAE leading to study discontinuation while four (1.3%) in NEAR-1 and two (0.7%) in NEAR-2 subjects reported a non-ocular TEAE leading to study discontinuation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the treatment effect consistency on the primary and key secondary efficacy endpoints of 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 four time points of Visit 3 (Day 8) was examined across the subgroups of age, gender, race, ethnicity, iris color, and baseline MRSE (Table 8 for the primary endpoint and Table 9 for the key secondary endpoints).

The analysis for the subgroups was conducted similarly as that for the other secondary endpoints, i.e., at each time point and post dose level, Orasis fitted a logistic regression model on the dichotomous response with baseline BDCVA (40 cm) and treatment group as explanatory variables for each category of each subgroup. Also, the reviewer fitted logistic regression models including baseline BDCVA (40 cm), treatment group, subgroup, and the treatment-by-subgroup interaction as exploratory variables to explore the heterogeneity of treatment effect across the subgroups. We did not have convincing evidence for treatment-by-subgroup interaction effects in odds. Additionally, we tested the interaction effects for the differences in response rates and came to the same conclusion.

As shown in Table 8 and Table 9, from both studies the percentages of being a responder in the CSF-1 group were all numerically greater than these in the vehicle group in all subgroups for the primary endpoint. The results for the key secondary endpoints are similar to these for the primary endpoint. In both studies, the proportion of responders was numerically greater than vehicle within subgroups at every time point on Day 8 except for some minorities (e.g., Asian, or other race) in race due to the small sample sizes. The results for these subgroup levels with small numbers might not be indicative of the overall treatment effects.

Table 8. Primary Endpoint across Subgroups: Percentage of Responders [a] in CSF-1 and Vehicle Groups by Subgroups at Visit 3 (Day 8)-One Hour Post Dose 1-Full Analysis Set (Observed Data Only)

Subgroup	NEAR-1		NEAR-2	
	CSF-1 n/m (%)	Vehicle n/m (%)	CSF-1 n/m (%)	Vehicle n/m (%)
Age group (years)				
45 to < 55	27/68 (39.7)	14/77 (18.2)	37/77 (48.1)	19/76 (25.0)
55 to 64	30/79 (38.0)	11/72 (15.3)	25/70 (35.7)	12/69 (17.4)
Sex				
Male	23/60 (38.3)	14/61 (23.0)	20/50 (40.0)	13/55 (23.6)
Female	34/87 (39.1)	11/88 (12.5)	42/97 (43.3)	18/90 (20.0)
Race				

Asian	1/6 (16.7)	0/14 (0)	4/5 (80.0)	0/7 (0)
Black or African American	7/24 (29.2)	4/25 (16.0)	2/13 (15.4)	0/9 (0)
White	48/114 (42.1)	20/106 (18.9)	55/126 (43.7)	30/127(23.6)
Other	1/3 (33.3)	1/4 (25.0)	1/3 (33.3)	1/2 (50.0)
Ethnicity				
Hispanic or Latino	11/32 (34.4)	5/23 (21.7)	13/29 (44.8)	6/25 (24.0)
Not Hispanic or Latino	46/115 (40.0)	20/126 (15.9)	49/118 (41.5)	25/120 (20.8)
Iris color in study eye				
Brown	24/80 (30.0)	12/85 (14.1)	26/69 (37.7)	11/66 (16.7)
Light	33/67 (49.3)	13/64 (20.3)	36/78 (46.2)	20/79 (25.3)
MRSE				
-4.5 D to <-0.5D	17/34 (50.0)	11/32 (34.4)	12/31 (38.7)	8/28 (28.6)
-0.5 D to ≤ 0.75D	29/84 (34.5)	9/87 (10.3)	42/87 (48.3)	15/86 (17.4)
> 0.75 D to 2.0 D	11/29 (37.9)	5/30 (16.7)	8/29 (27.6)	8/31 (25.8)

Abbreviations: BDCVA = best distance-corrected visual acuity; D = diopter; MRSE=manifest refraction spherical equivalent.
Note: n is the number of responders and m is the number of subjects with non-missing data at each time point within the visit. A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used to obtain inferential statistics.
[a] 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).

Table 9. Key Secondary Endpoints across Subgroups: Percentage of Responders [a] in CSF-1 and Vehicle Groups by Subgroups at Visit 3 (Day 8)- Full Analysis Set (Observed Data Only)

Subgroup	NEAR-1		NEAR-2	
	CSF-1 n/m (%)	Vehicle n/m (%)	CSF-1 n/m (%)	Vehicle n/m (%)
Two Hours Post Dose 1				
Age group (years)				
45 to < 55	24/68 (35.3)	13/77 (16.9)	36/77 (46.8)	15/76 (19.7)
55 to 64	34/79 (43.0)	12/72 (16.7)	24/70 (34.3)	15/69 (21.7)
Sex				
Male	20/60 (33.3)	14/61 (23.0)	19/50 (38.0)	11/55 (20.0)
Female	38/87 (43.7)	11/88 (12.5)	41/97 (42.3)	19/90 (21.1)
Race				
Asian	1/6 (16.7)	1/14 (7.1)	4/5 (80.0)	1/7 (14.3)
Black or African American	9/24 (37.5)	5/25 (20.0)	2/13 (15.4)	0/9 (0)
White	48/114 (42.1)	18/106 (17.0)	53/126 (42.1)	27/127 (21.3)
Other	0/3 (0)	1/4 (25.0)	1/3 (33.3)	2/2 (100)
Ethnicity				
Hispanic or Latino	11/32 (34.4)	7/23 (30.4)	16/29 (55.2)	7/25 (28.0)
Not Hispanic or Latino	47/115 (40.9)	18/126 (14.3)	44/118 (37.3)	23/120 (19.2)

Iris color in study eye				
Brown	28/80 (35.0)	16/85 (18.8)	33/69 (47.8)	13/66 (19.7)
Light	30/67 (44.8)	9/64 (14.1)	27/78 (34.6)	17/79 (21.5)
MRSE				
-4.5 D to <-0.5D	16/34 (47.1)	8/32 (25.0)	13/31 (41.9)	7/28 (25.0)
-0.5 D to ≤ 0.75D	28/84 (33.3)	11/87 (12.6)	37/87 (42.5)	16/86 (18.6)
>0.75 D to 2.0 D	14/29 (48.3)	6/30 (20.0)	10/29 (34.5)	7/31 (22.6)
One Hour Post Dose 2				
Age group (years)				
45 to < 55	34/68 (50.0)	13/77 (16.9)	45/77 (58.4)	14/76 (18.4)
55 to 64	36/79 (45.6)	10/72 (13.9)	32/70 (45.7)	10/69 (14.5)
Sex				
Male	30/60 (50.0)	12/61 (19.7)	26/50 (52.0)	10/55 (18.2)
Female	40/87 (46.0)	11/88 (12.5)	51/97 (52.6)	14/90 (15.6)
Race				
Asian	0/6 (0)	0/14 (0)	5/5 (100)	0/7 (0)
Black or African American	9/24 (37.5)	2/25 (8.0)	3/13 (23.1)	1/9 (11.1)
White	59/114 (51.8)	20/106 (18.9)	68/126 (54.0)	22/127 (17.3)
Other	2/3 (66.7)	1/4 (25.0)	1/3 (33.3)	1/2 (50.0)
Ethnicity				
Hispanic or Latino	15/32 (46.9)	4/23 (17.4)	17/29 (58.6)	6/25 (24.0)
Not Hispanic or Latino	55/115(47.8)	19/126(15.1)	60/118(50.8)	18/120(15.0)
Iris color in study eye				
Brown	30/80 (37.5)	12/85 (14.1)	34/69 (49.3)	8/66 (12.1)
Light	40/67 (59.7)	11/64 (17.2)	43/78 (55.1)	16/79 (20.3)
MRSE				
-4.5 D to <-0.5D	18/34 (52.9)	8/32 (25.0)	21/31 (67.7)	6/28 (21.4)
-0.5 D to ≤ 0.75D	37/84 (44.0)	10/87 (11.5)	46/87 (52.9)	12/86 (14.0)
>0.75 D to 2.0 D	15/29 (51.7)	5/30 (16.7)	10/29 (34.5)	6/31 (19.4)
Two Hours Post Dose 2				
Age group (years)				
45 to < 55	28/68 (41.2)	11/77 (14.3)	38/77 (49.4)	15/76 (19.7)
55 to 64	29/79 (36.7)	11/72 (15.3)	31/70 (44.3)	13/69 (18.8)
Sex				
Male	22/60 (36.7)	11/61 (18.0)	19/50 (38.0)	12/55 (21.8)
Female	35/87 (40.2)	11/88 (12.5)	50/97 (51.5)	16/90 (17.8)
Race				
Asian	1/6 (16.7)	0/14 (0.0)	3/5 (60.0)	1/7 (14.3)
Black or African American	6/24 (25.0)	3/25 (12.0)	2/13 (15.4)	1/9 (11.1)
White	49/114 (43.0)	18/106 (17.0)	63/126 (50.0)	25/127 (19.7)

Other	1/3 (33.3)	1/4 (25.0)	1/3 (33.3)	1/2 (50.0)
Ethnicity				
Hispanic or Latino	13/32 (40.6)	6/23 (26.1)	18/29 (62.1)	7/25 (28.0)
Not Hispanic or Latino	44/115 (38.3)	16/126 (12.7)	51/118 (43.2)	21/120 (17.5)
Iris color in study eye				
Brown	28/80 (35.0)	14/85 (16.5)	32/69 (46.4)	12/66 (18.2)
Light	29/67 (43.3)	8/64 (12.5)	37/78 (47.4)	16/79 (20.3)
MRSE				
-4.5 D to <-0.5D	14/34 (41.2)	9/32 (28.1)	16/31 (51.6)	6/28 (21.4)
-0.5 D to ≤ 0.75D	30/84 (35.7)	9/87 (10.3)	41/87 (47.1)	14/86 (16.3)
>0.75 D to 2.0 D	13/29 (44.8)	4/30 (13.3)	12/29 (41.4)	8/31 (25.8)

Abbreviations: BDCVA=best distance-corrected visual acuity; D=diopter; MRSE=manifest refraction spherical equivalent.
Note: n is the number of responders and m is the number of subjects with non-missing data at each time point within the visit. A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used to obtain inferential statistics.
[a] 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).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Orasis stated that "*All treatment comparisons for primary, secondary, and exploratory endpoints related to BDCVA were conducted with a logistic regression model including fixed effects of baseline BDCVA at 40 cm as a covariate and treatment. However, to assist the clinical interpretation, results are expressed in terms of percentages of responders in each treatment group with the treatment effect p-value from the logistic regression model*." It should be noted that the p-value from the logistic regression model was to compare the conditional odds ratio rather than the difference in percentages of responders in treatment groups. Also, Orasis's prespecified efficacy hypotheses were to compare the difference between study eyes treated with CSF-1 and study eyes treated with vehicle, in the percentage of responders.

To compare the differences of responders in CSF-1 and vehicle groups, we fitted the same logistic regression model as that from Orasis but used G-computation approach[4] to calculate the risk differences (95% CI) and the p-values for testing the differences for the primary and secondary endpoints. In general, the p-values for testing the differences of the percentages of responders in CSF-1 and vehicle groups were similar as that for testing the odds ratio and the inferences remained same.

[4] Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. *Drug Information Journal*: DIJ/Drug Information Association. 2011 Jul; 45:481-93.

5.2 Collective Evidence

In NEAR-1 study, CSF-1 was demonstrated to be significantly superior to vehicle, in achieving a ≥ 3-line (15-letter) gain in near BDCVA at 40 cm without a loss of 1 line or more in BDCVA at 4 m at all time points on Days 1, 8, and 15. In NEAR-2 study, the primary and all key secondary endpoints were met, as a significantly greater percentage of responders on Day 8. For all other secondary endpoints in NEAR-2 study, a similar trend effect was observed on Days 1 and Day 15. Hierarchal testing was stopped at five hours post Dose 2 (eight hours post dose 1) on Day 15 as the difference between CSF-1 and vehicle was not statistically significant compared to vehicle at this time point, as well as at four hours post Dose 2 (six hours post Dose 1) on Day 1. Despite the hierarchal testing, CSF-1 demonstrated a similar trend at all remaining time points for Days 1, 8 and 15, as the observed percentages of subjects with BDCVA improvement was consistently higher in CSF-1 treated subjects, with nominal p-values < 0.05 demonstrated at 20 out of 22 time points measured throughout the study.

5.3 Conclusions and Recommendations

Based on the collective efficacy evidence from the two adequate and well-controlled trials of NEAR-1 and NEAR-2 studies, we conclude 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.

5.4 Labeling Recommendations

In Section 14 of the draft labeling in the submission, Orasis proposed to include the text (in blue) below including the efficacy results from NEAR-1 and NEAR-2 (Table 1 and Figure 1).

The efficacy of Qlosi for the treatment of presbyopia was demonstrated in two Phase 3, randomized, double-masked, vehicle-controlled studies, namely NEAR 1 (NCT04599933) and NEAR 2 (NCT04599972). A total of 613 participants aged 45 to 64 years old with presbyopia were randomized (309 to Qlosi group) in these two studies. Participants were instructed to instill one drop of Qlosi or vehicle, in each eye, once in the morning and to repeat the instillation 2 to 3 hours later. Participants were treated for two weeks. Ophthalmic assessments were conducted on Day 1, 8 and 15 of the study at various timepoints. Responders demonstrated improvement by achieving a gain from baseline of 3 lines or more in near BDCVA at 40 centimeters without a loss of 1 line or more (≥ 5 letters) in BDCVA at 4 meters. Overall, the percentages of responders were consistently higher in the Qlosi group than in the Vehicle group at every assessment day (b) (4) (b) (4)

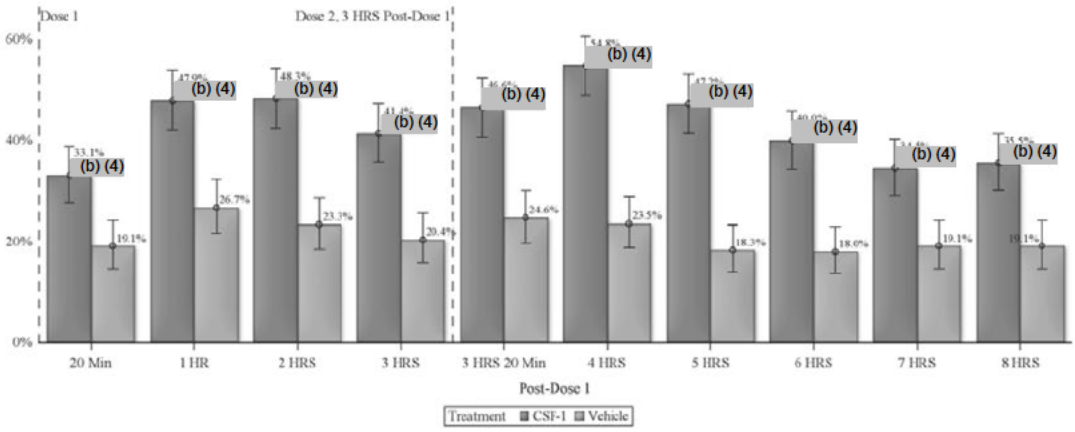
Table 1: Primary and key secondary results from NEAR-1 and NEAR-2 studies: Percentage of Responders - Day 8

	NEAR-1			NEAR-2		
Assessment timing	Qlosi N=155	Vehicle N=154	p-value	Qlosi N=154	Vehicle N=150	p-value
1 hour post Dose 1	(b) (4) %	16.9%	(b) (4)	41.6%	21.3%	(b) (4
2 hours post Dose 1	39.4%	16.9%		40.3%	20.7%	
1 hour post Dose 2	47.7%	15.6%		51.9%	16.7%	
2 hours post Dose 2	(b) (4) %	14.9%		46.1%	19.3%	

(b) (4)

Abbreviations: N: number of participants in this study arm

Figure 1 presents the percentage of responders for each time point at Day 15. (Standard analysis of pooled data NEAR-1 and NEAR-2)



Abbreviations: HRS: hours; min: minutes, CSF-1: development code name for Qlosi™.

This figure demonstrates the onset of the Qlosi effect on presbyopia, from 20 minutes post dose 1, and lasting up to 8 hours.

Reviewer's Remark: *Overall, the Applicant's proposed text included in Section 14 of the draft label appears reasonable. However, in Table 1 Orasis only presented p-values. We recommend that 95% confidence intervals be used instead as promotions should not focus on the p-values but rather the range of the effect sizes. Also, we recommend that Orasis present the 95% confidence intervals for comparing the difference of the percentages of responders between CSF-1 and vehicle groups as they prespecified in Table 1 and Figure 1.*

6. APPENDIX

Sensitivity Results for the Primary Endpoint

Table 10. Visit 3 (Day 8): Primary Efficacy Sensitivity 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 (Observed Data Only)

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]	57 (38.8)	25 (16.8)	62 (42.2)	31 (21.4)
Number (%) of non-responders	90 (61.2)	124 (83.2)	85 (57.8)	114 (78.6)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.0 (1.7, 5.2)		3.0 (1.7, 5.0)	
p-value [b]	0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	19.5 (9.8, 29.2)		21.8 (11.7, 32.0)	
p-value [c]	<0.0001		<0.0001	

Abbreviations: BDCVA = best distance corrected visual acuity; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study.

Note: N is the number of analyzed subjects in each arm. Denominators for percentages are the number of subjects with no missing data at Visit 3 (Day 8) 1-hour post Dose 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) with no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m).

[b] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation to calculate the risk difference and p-value for the comparison of the risk difference.

Source: Table 14.2.1.2 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 11. Primary Efficacy Sensitivity 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 (All Missing Data Imputed as Failure)

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]	57 (36.8)	25 (16.2)	62 (40.3)	31 (20.7)
Number (%) of non-responders	98 (63.2)	129 (83.8)	92 (59.7)	119 (79.3)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	2.9 (1.6, 5.0)		2.9 (1.7, 4.9)	
p-value [b]	0.0002		<0.0001	
Risk difference (%, 95% CI) [c]	18.4 (9.0, 27.7)		21.0 (11.2, 30.9)	
p-value [c]	0.0001		<0.0001	

Abbreviations: BDCVA = best distance corrected visual acuity; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study.

Note: N is the number of analyzed subjects in each arm and is the denominator for percentages. A subject with missing response at Visit 3 (Day 8) was imputed as "Failure" (i.e., non-responder).

[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] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.1.3 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 12. Primary Efficacy Sensitivity 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, PPS (Observed Data Only)

Parameter statistics	**20-150-0002 (NEAR-1)**		**20-150-0003 (NEAR-2)**	
	CSF-1 (N=149)	**Vehicle (N=144)**	**CSF-1 (N=147)**	**Vehicle (N=145)**
Number (%) of responders [a]	56 (39.2)	24 (17.0)	60 (42.9)	30 (21.4)
Number (%) of non-responders	87 (60.8)	117 (83.0)	80 (57.1)	110 (78.6)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.0 (1.7, 5.4)		3.0 (1.7, 5.2)	
p-value [b]	0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	20.1 (10.2, 30.0)		22.3 (11.9, 32.7))	
p-value [c]	<0.0001		<0.0001	

Abbreviations: BDCVA = best distance corrected visual acuity; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study.

Note: N is the number of analyzed subjects in each arm. Denominators for percentages are the number of subjects with no missing data.

[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] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.1.4 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 13. Primary Efficacy Sensitivity 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 (Tipping Point Analysis)

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]	57 (36.8)	30 (19.5)	62 (40.3)	36 (24.0)
Number (%) of non-responders	98 (63.2)	124 (80.5)	92 (59.7)	114 (76.0)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	2.3 (1.3, 3.8)		2.4 (1.4, 4.0)	
p-value [b]	0.0027		0.0008	
Risk difference (%, 95% CI) [c]	15.0 (5.4, 24.6)		17.8 (7.8, 27.9)	
p-value [c]	0.0021		0.0005	

Abbreviations: BDCVA = best distance corrected visual acuity; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study.

Note: In this extreme case of tipping point analysis, missing value in CSF-1 (NEAR-1: 8; NEAR-2: 7) was set to failure and missing value in vehicle (NEAR-1: 5; NEAR-2: 5) was set to success. N in the header is the number of analyzed subjects in that treatment arm. Denominators for percentages are the number of subjects with no missing data.

[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] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables is used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.1.5 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 14. Visit 3 (Day 8): Key Secondary Efficacy Sensitivity 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), FAS (Observed Data Only)

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)
2-Hour Post-Dose 1				
Number (%) of responders [a]	58 (39.5)	25 (16.8)	60 (40.8)	30 (20.7)
Number (%) of non-responders	89 (60.5)	124 (83.2)	87 (59.2)	115(79.3)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.1 (1.8, 5.3)		2.8 (1.7, 4.8)	
p-value [b]	<0.0001		0.0001	
Risk difference (%, 95% CI) [c]	20.4 (10.7, 30.2)		20.9 (10.8, 31.1)	
p-value [c]	<0.0001		<0.0001	
1-Hour Post-Dose 2				
Number (%) of responders [a]	70 (47.6)	23 (15.4)	77 (52.4)	24 (16.6)
Number (%) of non-responders	77 (52.4)	126 (84.6)	70 (47.6)	121(83.4)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	4.8 (2.7, 8.5)		6.1 (3.5, 10.6)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	29.9 (20.1, 39.8)		36.6 (26.7, 46.5)	
p-value [c]	<0.0001		<0.0001	
2-Hour Post-Dose 2				
Number (%) of responders [a]	57 (38.8)	22 (14.8)	69 (46.9)	28 (19.3)
Number (%) of non-responders	90 (61.2)	127 (85.2)	78 (53.1)	117(80.7)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.5 (2.0, 6.2)		4.2 (2.4, 7.3)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	21.8 (12.3, 31.3)		28.8 (18.8, 38.8)	
p-value [c]	<0.0001		<0.0001	

Abbreviations: BDCVA = Best Distance Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment of Diabetic Retinopathy Study.

Note: N is the number of analyzed subjects in each arm. Denominators for percentages are the number of subjects with no missing data at each visit.

[a] 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).

[b] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables are used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.2.2 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 15. Visit 3 (Day 8): Key Secondary Efficacy Sensitivity 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), FAS (All Missing Data Imputed as Failure)

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)
2-Hour Post-Dose 1				
Number (%) of responders [a]	58 (37.4)	25 (16.2)	60 (39.0)	30 (20.0)
Number (%) of non-responders	97 (62.6)	129 (83.8)	94 (61.0)	120(80.0)
Comparison (CSF-1 vs. vehicle)				
Odds ratio [b] (95% CI)	2.9 (1.7, 5.1)		2.8 (1.6, 4.7)	
p-value [b]	0.0001		0.0001	
Risk difference (%, 95% CI) [c]	19.2 (9.8, 28.6)		20.1 (10.2, 30.0)	
p-value [c]	<0.0001		<0.0001	
1-Hour Post-Dose 2				
Number (%) of responders [a]	70 (45.2)	23 (14.9)	77 (50.0)	24 (16.0)
Number (%) of non-responders	85 (54.8)	131 (85.1)	77 (50.0)	126(84.0)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	4.6 (2.6, 8.0)		5.9 (3.4, 10.3)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	28.2 (18.7, 37.8)		35.1 (25.5, 44.8)	
p-value [c]	<0.0001		<0.0001	
2-Hour Post-Dose 2				
Number (%) of responders [a]	57 (36.8)	22 (14.3)	69 (44.8)	28 (18.7)
Number (%) of non-responders	98 (63.2)	132 (85.7)	85 (55.2)	122(81.3)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.3 (1.9, 5.9)		4.1 (2.4, 7.2)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	20.6 (11.4, 29.8)		27.7 (18.0, 37.4)	
p-value [c]	<0.0001		<0.0001	

Abbreviations: BDCVA = Best Distance Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment of Diabetic Retinopathy Study.

Note: N is the number of analyzed subjects in each arm and is the denominator for percentages. A subject whose response is missing at visit 3 (Day 8) is singly imputed as being "Failure" (i.e., non-responder).

[a] 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).

[b] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables are used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.2.3 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 16. Visit 3 (Day 8): Key Secondary Efficacy Sensitivity 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), PPS (Observed Data Only)

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)
2-Hour Post-Dose 1				
Number (%) of responders [a]	57 (39.9)	24 (17.0)	59 (42.1)	29 (20.7)
Number (%) of non-responders	86 (60.1)	117 (83.0)	81 (57.9)	111 (79.3)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.1 (1.8, 5.5)		3.0 (1.7, 5.1)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	21.0 (11.1, 31.0)		22.1 (11.7, 32.6)	
p-value [c]	<0.0001		<0.0001	
1-Hour Post-Dose 2				
Number (%) of responders [a]	69 (48.3)	21 (14.9)	75 (53.6)	23 (16.4)
Number (%) of non-responders	74 (51.7)	120 (85.1)	65 (46.4)	117 (83.6)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	5.3 (3.0, 9.6)		6.4 (3.6, 11.3)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	31.4 (21.5, 41.3)		37.8 (27.7, 47.9)	
p-value [c]	<0.0001		<0.0001	
2-Hour Post-Dose 2				
Number (%) of responders [a]	56 (39.2)	22 (15.6)	67 (47.9)	27 (19.3)
Number (%) of non-responders	87 (60.8)	119 (84.4)	73 (52.1)	113(80.7)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.4 (1.9, 6.0)		4.4 (2.5, 7.6)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	21.8 (12.0, 31.7)		29.5 (19.3, 39.8)	
p-value [c]	<0.0001		<0.0001	

Abbreviations: BDCVA = Best Distance Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment of Diabetic Retinopathy Study.

Note: N is the number of analyzed subjects in each arm. Denominators for percentages are the number of subjects with no missing data at each visit.

[a] 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).

[b] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables are used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.2.4 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

Table 17. Visit 3 (Day 8): Key Secondary Efficacy Sensitivity 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), FAS (Tipping Point Analysis)

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)
2-Hour Post-Dose 1				
Number (%) of responders [a]	58 (37.4)	30 (19.5)	60 (39.0)	35 (23.3)
Number (%) of non-responders	97 (62.6)	124 (80.5)	94 (61.0)	115(76.7)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	2.3 (1.4, 3.9)		2.3 (1.4, 3.8)	
p-value [b]	0.0017		0.0015	
Risk difference (%, 95% CI) [c]	15.9 (6.2, 25.2)		16.9 (6.8, 27.0)	
p-value [c]	0.0013		0.0010	
1-Hour Post-Dose 2				
Number (%) of responders [a]	70 (45.2)	28 (18.2)	77 (50.0)	29 (19.3)
Number (%) of non-responders	85 (54.8)	126 (81.8)	77 (50.0)	121(80.7)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	3.6 (2.1, 6.1)		4.7 (2.7, 8.0)	
p-value [b]	<0.0001		<0.0001	
Risk difference (%, 95% CI) [c]	24.9 (15.1, 34.7)		31.9 (22.0, 41.8)	
p-value [c]	<0.0001		<0.0001	
2-Hour Post-Dose 2				
Number (%) of responders [a]	57 (36.8)	27 (17.5)	69 (44.8)	33 (22.0)
Number (%) of non-responders	98 (63.2)	127 (82.5)	85 (55.2)	117(78.0)
Comparison (CSF-1 vs. vehicle)				
Odds ratio (95% CI) [b]	2.6 (1.5, 4.5)		3.4 (2.0, 5.7)	
p-value [b]	0.0006		<0.0001	
Risk difference (%, 95% CI) [c]	17.2 (7.7, 26.7)		24.5 (14.6, 34.4)	
p-value [c]	0.0004		<0.0001	

Abbreviations: BDCVA = Best Distance Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment of Diabetic Retinopathy Study.

Note: N in the header is the number of analyzed subjects in that treatment arm and is the denominator for percentages. Missing value in CSF-1 was set to failure and missing value in vehicle was set to success.

[a] 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).

[b] A logistic regression model on the dichotomous response with treatment group and baseline BDCVA (40 cm) as explanatory variables are used to obtain inferential statistics. p-value is presented for the main effect of treatment group using Wald statistics.

[c] Based on the same logistic regression model above, the reviewer used G-computation approach to calculate the risk difference and p-value.

Source: Table 14.2.2.5 in the Clinical Report for NEAR-1 and NEAR-2 studies and reviewer's analyses for the risk difference.

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