[redacted]

STATISTICAL ANALYSIS PLAN (SAP)

A Multi-Center, Double-Masked Evaluation of the Efficacy and Safety of CSF-1 in the Treatment of Presbyopia

Sponsor: Orasis Pharmaceuticals, Ltd

Protocol Number: 18-150-0006 (Phase 2b)

Author: [redacted]

Date: 24 July 2019

Version: 1.0

[redacted]

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SAP Preparation, Review, and Approvals

Prepared by: [redacted] 24 Jul 2019
Date

Reviewed by: [redacted] 24 Jul 2019
Date

Approved by: [redacted] _____
Date

Approved by: [redacted] _____
Date

Orasis Pharmaceuticals, Ltd

[redacted]

[redacted]

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SAP Preparation, Review, and Approvals

Prepared by: [redacted]

Reviewed by: [redacted]

Approved by: [redacted] 7/30/2019 DT

Date

Approved by: [redacted] 7/24/2019

Date

Orasis Pharmaceuticals, Ltd

[redacted]

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	*Bis in die* (Twice Daily)
CI	Confidence Interval
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	Manifest Refraction Spherical Equivalent
NCS	Not Clinically Significant
PP	Per Protocol
mPP	Modified Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
WHO	World Health Organization

[redacted]

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol 18-150-0006, Phase 2b, Amendment 2 dated 05 June 2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. Any additional analyses required to supplement the planned analyses described in this SAP will be duly noted in the clinical study report.

2. Study Objectives

The primary objective of this study is to evaluate the efficacy of CSF-1 for the treatment of presbyopia.

The secondary objectives of this study are to evaluate the safety, tolerability, [redacted] of CSF-1 versus the individual components (pilocarpine hydrochloride and diclofenac sodium 0.006%) for the treatment of presbyopia at two concentrations (0.2% or 0.4% pilocarpine hydrochloride).

2.1 Study Variables

For all study variables, baseline is defined as the pre-randomization measurement taken at Visit 2 (Day 1). If the measurement is not available from Visit 2 (Day 1), then the measurement from screening Visit 1 (Day -1 to -14) will be used as baseline for all treatments/visits. Change from baseline will be calculated as follow-up measure minus baseline measure.

Efficacy variables include monocular and binocular best corrected visual acuity (BCVA) at 40 cm, [redacted]

Safety variables include BCVA at distance under normal and low luminance testing conditions, slit lamp biomicroscopy measures, conjunctival redness grading and investigational product (IP) drop comfort assessment, as well as intraocular pressure (IOP) and adverse events (AE). The logarithm of the minimum angle of resolution (logMAR) units will be used for all VA safety and efficacy measures. Visual acuity will be assessed with best distance-correction determined by the manifest refraction at Visit 1 (Day -1 to -14). Please refer to the BCVA protocol for conducting manifest refraction procedures.

[redacted]

2.2 Primary Variable

The percentage of study eyes with a ≥3-line (15 letter) gain from baseline (Day 1) in BCVA at 40 cm, 1-hour post-treatment at Day 8 and Day 15.

2.3 Secondary Variables

The secondary efficacy variables include the following:

- [redacted]
- Percentage of study eyes with a ≥2-line (10 letter) gain from baseline (Day 1) in BCVA at 40 cm [redacted] 1 hour, [redacted] post-treatment at Day 8 and Day 15
- [redacted]
  15

2.4 Safety Variables

The safety variables include the following:

- BCVA
- Best corrected low luminance distance VA
- Findings from slit lamp biomicroscopy examination
- Conjunctival redness grading
- IP drop comfort assessment
- IOP measurements
- Incidence of AEs (reported, elicited, and observed)

2.5 Statistical Hypotheses

The null and alternative hypotheses, based on the study objectives and primary variable, are as follows:

H_{01}: The difference, between study eyes treated with CSF-1 (0.4%/0.006%) and study eyes treated with diclofenac sodium (0.006%), in the percentage of study eyes with a ≥3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment = 0.

H_{11}: The difference, between study eyes treated with CSF-1 (0.4%/0.006%) and study eyes treated with diclofenac sodium (0.006%), in the percentage of study eyes with a ≥3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment $\neq$ 0.

[redacted]

H_{02}: The difference, between study eyes treated with Pilocarpine (0.4%) and study eyes treated with diclofenac sodium (0.006%), in the percentage of study eyes with a ≥3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment = 0.

H_{12}: The difference, between study eyes treated with Pilocarpine (0.4%) and study eyes treated with diclofenac sodium (0.006%), in the percentage of study eyes with a ≥3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment ≠ 0.

[redacted]

3. Study Design and Procedures

3.1 Overall Study Design

This is a 4-visit randomized, double-masked, multi-center, parallel-group study evaluating the safety and efficacy of CSF-1 compared with pilocarpine hydrochloride alone and diclofenac sodium (0.006%) alone in approximately 150 subjects with presbyopia.

Visit 1 (Day -1 to -14): Subjects will be screened through ophthalmic assessments and both near and distance BCVA tests. [redacted]

Visit 2 (Day 1): Pre-treatment ophthalmic assessments will be repeated at Visit 2. Following the pre-treatment assessments, qualified subjects will be randomized to 1:1:1 to one of the following treatment arms:

- CSF-1: pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose]) and diclofenac sodium (0.006%)
- Pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose])
- Diclofenac sodium (0.006%)

All subjects will be instructed to dose each eye twice daily ([redacted] in both eyes with a single drop for approximately 1 week until the afternoon before study Visit 3. Subjects randomized to the CSF-1 arm will receive pilocarpine hydrochloride 0.2%/diclofenac sodium 0.006% (CSF-1 low dose); subjects randomized to the pilocarpine hydrochloride alone arm will receive pilocarpine hydrochloride (0.2%) alone; and, subjects randomized to diclofenac sodium alone arm will dose with diclofenac sodium (0.006%) alone.

Visit 3 (Day 8 ± 2): Pre-treatment ophthalmic assessments will be repeated at Visit 3. The morning dose of IP will be administered by study site personnel followed by ophthalmic safety and efficacy assessments [redacted] After the Visit 3 assessments, subjects will continue BID dosing ([redacted]) in both eyes for approximately 1 week.

Subjects initially randomized to the CSF-1 arm will now receive pilocarpine hydrochloride 0.4%/diclofenac sodium 0.006% (CSF-1 high dose); subjects randomized to the pilocarpine hydrochloride alone arm will now receive pilocarpine hydrochloride (0.4%) alone; and, subjects randomized to diclofenac sodium alone arm will continue dosing with diclofenac sodium (0.006%) alone.

Visit 4 (Day 15 ± 2): Pre-treatment ophthalmic assessments will be repeated at Visit 4. The morning dose of IP will be administered by study site personnel followed by ophthalmic safety and efficacy assessments [redacted]. After the Visit 4 assessments, subjects will subsequently exit the study.

Figure 1 provides a graphical representation of the study design and study visitation.

Study visits will be referred to in all tables and listings as the planned study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 shows the scheduled study visits, their planned study day, and the acceptable visit window for each study visit:

Table 1. Scheduled Study Visits

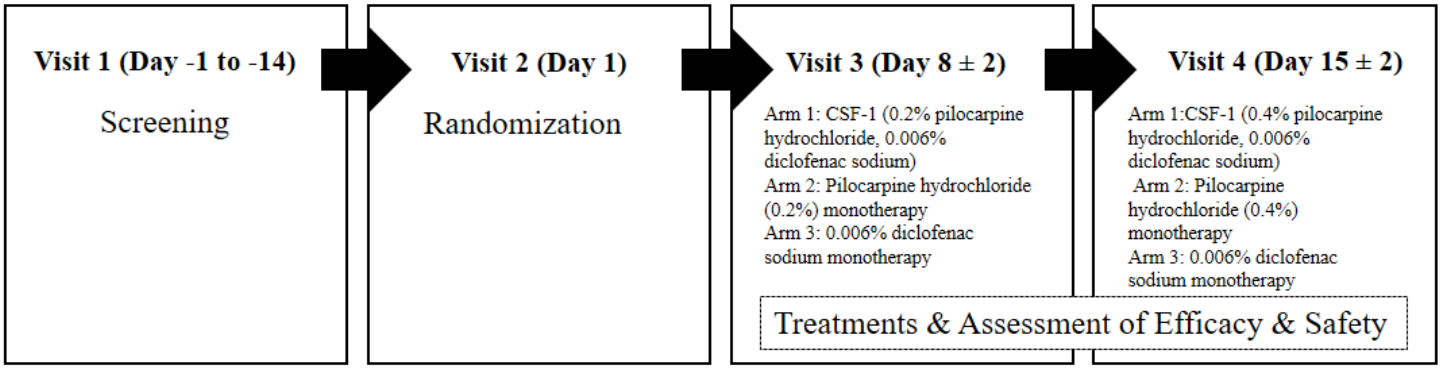
Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -1 to -14	N/A
Visit 2	Day 1	N/A
Visit 3	Day 8	+/- 2 Days
Visit 4	Day 15	+/- 2 Days

3.2 Schedule of Visits and Measurements

The schedule of visits and assessments is provided in Table 2.

[redacted]

Figure 1. Study Design and Study Visitation

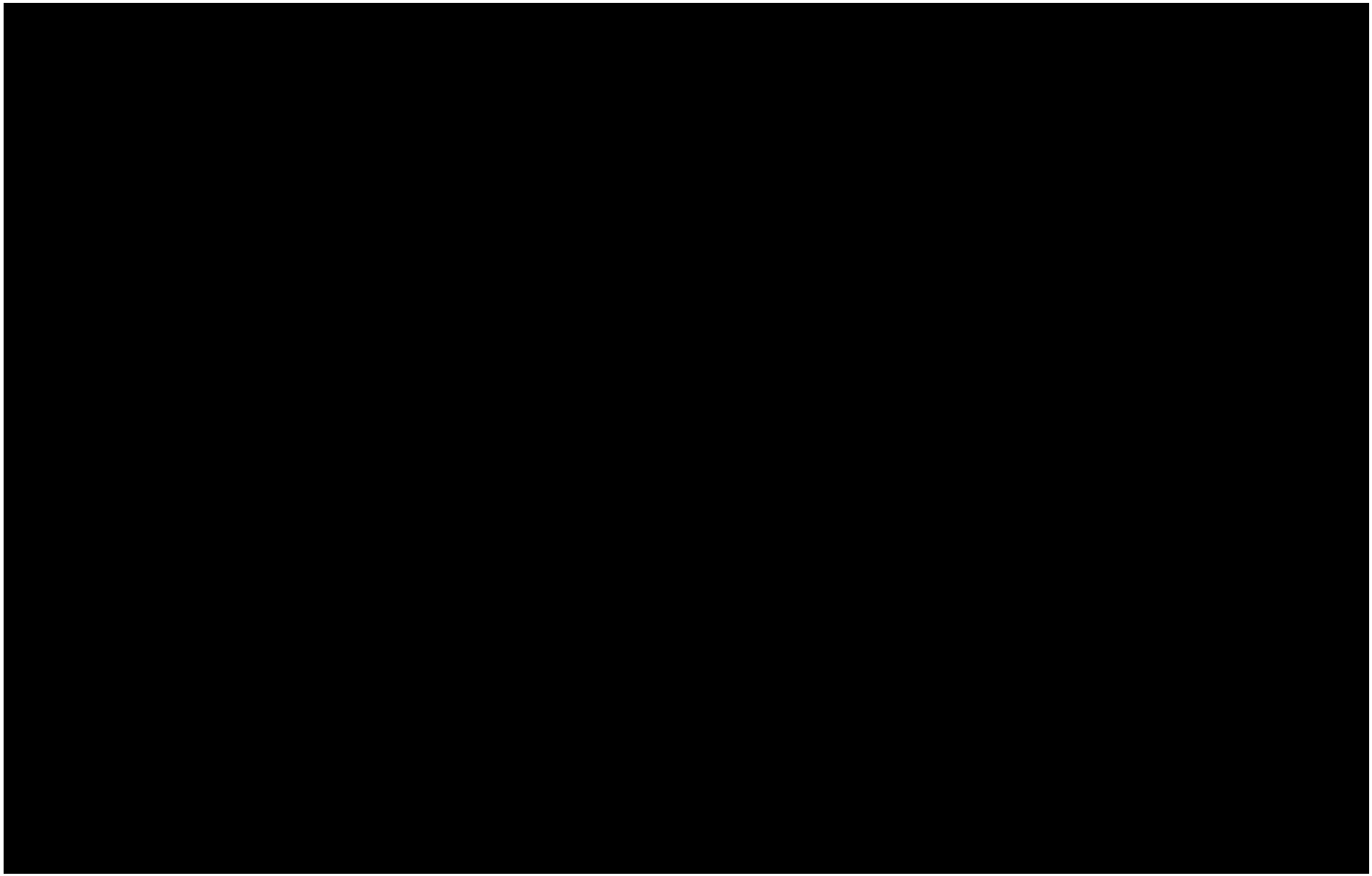


[redacted]

Table 2. Schedule of Visits and Assessments

[redacted]

[redacted]



4. Study Treatments

The IP is CSF-1, a topical eye drop solution for [redacted] presbyopia, which works by reducing the natural pupil size and correspondingly increasing the depth of field. The formulation developed by Orasis Pharmaceuticals Ltd. is a viscous eye drop containing the active ingredients pilocarpine hydrochloride and diclofenac sodium with the addition of excipients, [redacted]. The inclusion of a non-steroidal anti-inflammatory drug (diclofenac sodium) may reduce the inflammatory response induced by pilocarpine hydrochloride. Pre-treatment ophthalmic assessments will be repeated at Day 1. Following the pre-treatment assessments, qualified subjects will be randomized to 1:1:1 to one of the following treatment arms:

- CSF-1: pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose]) and diclofenac sodium (0.006%)
- Pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose])
- Diclofenac sodium (0.006%)

After randomization, subjects will receive IP and a dosing diary. Once dispensed to the subject, IP [redacted] Subjects will be instructed to save and return all used and unused IP and to bring their kits to each study visit. Subjects will be instructed to dose bilaterally BID in the morning and afternoon ([redacted] and record doses in their diary (paper). Subjects should not dose before the morning of Day 8. At Day 8, subjects will receive their morning dose from study site personnel, after the required pre-treatment assessments, and the current IP will be collected.

Subjects will be assigned a new IP at the conclusion of Day 8 and instructed on the use of a new dosing diary. The afternoon dose, from the new IP, will be instilled in-office during Day 8. After subjects receive their IP and dosing diary, subjects will be instructed to dose bilaterally BID in the morning and afternoon ([redacted]) and record doses in their diary until Day 15. Subjects should not dose before the morning of Day 15. At Day 15, subjects will receive their last dose from study site personnel, after the required pre-treatment assessments, and the current IP will be collected. Subjects will exit the study after all assessments are complete at Day 15.

4.1 Method of Assigning Subjects to Treatment Groups

At Visit 1 (Day -1 to -14), each subject who signs an informed consent form (ICF) will be assigned a subject number (a five-digit number starting with the 2-digit site number followed by a sequential three-digit number starting with 001). The five-digit subject number will be used to identify subjects in all datasets and listings for this study. Once a subject meets all qualification criteria at Day 1, they will be randomized in a 1:1:1 ratio via an interactive response technology system to one of three treatment groups: A, CSF-1; B, pilocarpine hydrochloride alone; C, diclofenac sodium alone; and stratified by iris color (brown versus light [i.e. blue, green, gray, and hazel]) and by baseline manifest refraction spherical equivalent ([redacted]

; randomization will not be stratified by site. Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known (e.g. iris color and baseline characteristics) and unknown subject attributes are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.

4.2 Masking and Unmasking

An independent, unmasked biostatistician who is not otherwise involved in the trial will generate the complete randomized study drug kit list. The subject, study sponsor, medical investigators, and study staff will be masked during the entire randomization process and throughout the course of the study. When medically necessary, the investigator may need to determine what treatment has been assigned to a particular subject. When possible (i.e., in non-emergent situations), and/or the study sponsor should be notified before unmasking the IP. In emergency situations, the investigator must notify the sponsor within 24 hours after determining that it is necessary to unmask the treatment assignment. The investigator must also indicate in source documents and in the electronic case report form (eCRF) that the mask was broken and provide the date, time, and reason for breaking the mask.

5. Sample Size and Power Considerations

Fifty subjects per each of the three treatment arms (150 total), yields an 85% power to establish the superiority of CSF-1 (0.4%/0.006%) and Pilocarpine (0.4%) to diclofenac sodium (0.006%) alone in the percentage of study eyes demonstrating a ≥3-line (15-letter) gain in BCVA at 40 cm, 1-hour post-treatment from the baseline measurement using a Pearson chi-squared test at a 2-sided $\alpha = 0.05$, assuming that the diclofenac sodium (0.006%) alone response is 5% and the CSF-1 response is 27%, resulting . At least approximately 30% of subjects should have a light (i.e. blue, green, gray, and hazel) iris and at least approximately 30% should have a brown iris. The actual iris proportions will vary based on the actual subjects enrolled and treated.

6. Data Preparation

All reported study data will be recorded on the eCRFs supplied by using . Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF. After data are entered into the clinical study database, electronic edit checks, and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the sponsor and . in consultation with .

The final analyses outlined in this document will be carried out only after the following have occurred:

- All data management requirements are met according to [redacted] standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate [redacted] and sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7. Analysis Sets

7.1 Intent-to-Treat

The intent-to-treat analysis set (ITT) will include all randomized subjects. Subjects in the ITT will be analyzed as randomized.

7.2 Per Protocol

The per protocol (PP) set will include subjects in the ITT who do not have significant protocol deviations that affect the primary endpoint. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP set will be analyzed as treated.

7.3 Modified Per Protocol

[redacted]

7.4 Safety

The safety set will include all subjects who have received at least one dose of the IP. Subjects in the safety analysis set will be analyzed as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

The study eye will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables. The study eye will be defined as the eye that meets all enrollment criteria. If both eyes meet all enrollment criteria,

then the eye with the worse Day 1 BCVA at 40 cm will be the study eye. If both eyes have the same BCVA at 40 cm, then the right eye will be deemed the study eye.

8.2 Missing Data Handling and Sensitivity Analysis

All analyses, including the primary efficacy analysis described in Section 12.1, will include observed data only.

8.3 Definition of Baseline

For all variables, baseline is defined as the pre-randomization measurement taken at Visit 2 (Day 1). If the measurement is not available from Visit 2 (Day 1), then the measurement from screening Visit 1 (Day -1 to -14) will be used as baseline for all treatments/visits. Change from baseline will be calculated as: Follow-up Measure – Baseline Measure.

8.4 Data Analysis Conventions

All data analysis will be performed by after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using . Output will be provided in rich text format for tables and portable document format for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations, arithmetic mean, standard deviation, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to 1 additional decimal place than reported in the raw values. Standard deviations will be presented to 2 additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to 1 decimal place (i.e., XX.X%). Change from baseline will be calculated as baseline subtracted from the relevant follow-up visit (Follow-up Visit – Baseline Visit), with baseline defined in Section 8.3 of this SAP.

All statistical tests, unless otherwise indicated, will be 2-sided with a significance level of 0.05 ($\alpha = 0.05$). Confidence intervals (CI) for differences between treatment groups will be 2-sided at 95% confidence. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999.”

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit.

[redacted]

8.5 Adjustment for Multiplicity

For the primary statistical hypotheses described in Section 2.5 of this SAP, the study will be considered a success if either of the null hypotheses, H_{01} or H_{02}, are rejected in favor of their corresponding alternative hypotheses, H_{11} or H_{12}. Rejecting H_{01} and/or H_{02} implies that CSF-1 (0.4%/0.006%) and/or Pilocarpine (0.4%) are signficantly ($\alpha = 0.05$) better than diclofenac sodium (0.006%), provided that the differencefavors CSF-1 and/or Pilocarpine, in achieving a ≥3-line (15 letter) gain from baseline in BCVA at 40 cm (1-hour post-treatment). This primary efficacy variable was specifically selected to align with the primary objective of the study: to evaluate the efficacy of CSF-1 for the treatment of presbyopia.

The overall Type I error of the 2-sided $\alpha = 0.10$ will be preserved through the use of Bonferroni correction procedures testing each hypothesis individually at a 2-sided $\alpha = 0.05$. If H_{01} is rejected and CSF-1 (0.4%/0.006%) is considered a success, then CSF-1 (0.2%/0.006%) will be tested against diclofenac sodium (0.006%) at a 2-sided $\alpha = 0.05$. Similarly, if H_{02} is rejected and Pilocarpine (0.4%) is considered a success, then Pilocarpine (0.2%) will be tested against diclofenac sodium (0.006%) at a 2-sided $\alpha = 0.05$. Within these hierarchical frameworks, these hypotheses can be tested at a 2-sided $\alpha = 0.05$ while still preserving an overall Type I error of $\alpha = 0.10$. For this Phase 2 study, all secondary and safety endpoints will be tested without adjustment for multiplicity.

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. A discontinued subject is someone who does not complete the four protocol-defined study visits. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment arm for all randomized subjects. The reasons for study discontinuation will also be summarized and include: AE, lost to follow-up, physician decision, protocol violation, study terminated by sponsor, withdrawal by subject, and other. A subject listing will be provided which includes the date and reason for study discontinuation.

The number of subjects in each of the analysis sets (ITT, PP, and Safety) will be displayed by treatment arm, with the number of subjects and percentages calculated using randomized subjects as the denominator. [redacted]. The number and percentage of subjects with major protocol deviations, which could affect analysis of the primary endpoint, will be summarized by treatment arm and overall for all randomized subjects. Protocol deviations will be classified as major or minor prior to the closure of the database during a masked review of each protocol deviation. Major deviations will be defined as those deviations that potentially affect the analysis of the primary study endpoint.

A subject listing will be provided which includes the date of the deviation, the deviation code and description, and the classification of whether the deviation was deemed major or minor. In addition, subject listings will include treatment arm and ICF signature date, and exclusions from the PP set.

10. Demographic and Baseline Characteristics

10.1 Demographics

The subject demographic data collected in this study include age, sex, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as Multi-Racial, and subjects who record more than one iris color will be classified as heterochromia. Sex, race, ethnicity, and iris color will be presented using descriptive summary statistics with frequency counts and percentages. Age (years) will be summarized, overall and by treatment arm, using continuous descriptive statistics. Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

Demographic variables will be summarized for the ITT and PP by treatment arm and overall in tables.

A subject listing that includes all demographic variables will also be provided.

10.2 Baseline Characteristics

Baseline characteristics are measured to ensure the safety and eligibility of subjects at Visit 1 (Day -1 to -14) and to confirm their previous results obtained within three months of Visit 1 (Day -1 to -14) have not changed significantly. Subject level listings will be used to present pre-treatment information from the ITT analysis set at the eye level when appropriate. Baseline characteristics will be contained in subject listings only and will include:

- Manifest refraction
- Dark-adapted pupillometry
- Fluorescein staining
- Dilated indirect funduscopy

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment arm at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the Safety analysis set. Ocular medical history will be similarly summarized at the subject level. If a subject reports the same PT multiple times within the same SOC, then that PT will only be reported once within that SOC. As

with the PT, if a subject reports multiple conditions within the same SOC, then that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular information.

11.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (WHODrug Global, B3, September 2018) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name (generic drug name). If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be employed. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (eg, multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug. Prior medications are defined as those medications not concomitant, but taken within 30 days of screening Visit 1. Prior and concomitant medications will be summarized using the Safely analysis set. Medications will be tabulated for each treatment arm using frequency counts and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if reporting one or more medications. Percentages will be based on the number of subjects in each treatment arm.

Summaries will be generated separately for prior and concomitant medications, with ocular and non-ocular data also summarized separately. Subject listings will group prior and concomitant medications together, with ocular and non-ocular information presented separately.

12. Efficacy Analyses

12.1 Primary Efficacy Analysis

The primary efficacy variable in this study is the percentage of study eyes with a ≥3-line (15 letter) gain from baseline (Day 1) in monocular BCVA at 40 cm, one-hour post-treatment at Day 8 and Day 15. Early Treatment of Diabetic Retinopathy Study format VA charts will be employed to assess VA at all ranges. All VA measurements will be assessed via best distance-correction determined by the manifest refraction at screening Visit 1. The primary efficacy analysis of the primary efficacy variable will utilize the PP analysis set on observed data only.

The primary analyses will be completed using [redacted] to maintain the overall Type I error, as detailed in Section 8.5 of this SAP, with statistical inference made on the comparisons between CSF-1 (0.4%/0.006%) versus diclofenac sodium (0.006%) and between Pilocarpine (0.4%) versus diclofenac

sodium (0.006%). As also detailed in the Section 8.5, only if the higher dose concentrations for CSF-1 (0.4%/0.006%) and/or Pilocarpine (0.4%) are successful will the corresponding lower dose concentrations for CSF-1 (0.2%/0.006%) and/or Pilocarpine (0.2%), respectively, have inference made on the statistical test.

Standard errors and CIs (90% and 95%) will also be presented for each treatment group and the difference between treatment groups.

[redacted]

[redacted]

12.2 Secondary Efficacy Analysis

The key secondary efficacy analysis will be the same analysis as the primary analysis, but instead employing the ITT analysis set.

[redacted]

For the assessment of BCVA at 40 cm, the percentage of study eyes achieving a ≥3-line (15-letters) and ≥2-line (10-letters) improvement from baseline for [redacted] 1 [redacted] hours post-treatment) will be conducted using the PP analysis set. [redacted] analyses of these secondary efficacy variables will then be repeated using the ITT analysis set. [redacted] The observed BCVA as well as the change from baseline in BCVA will be summarized by treatment group using continuous descriptive summary statistics, and subject-specific BCVA data will also be presented in a listing for each visual range, separately.

[redacted]

[redacted]

13. Exploratory Analysis

[redacted]ther.

14. Safety Analyses

All safety analyses will be conducted using the safety analysis set. BCVA at distance under normal and low luminance testing conditions, findings from slit lamp biomicroscopy examination, conjunctival redness grading and IP drop comfort assessment, as well as IOP measurements will be summarized descriptively

using quantitative and qualitative summary statistics by treatment arm and subject visit, as appropriate. All such measurements related to safety endpoints will also be presented in a detailed subject listing.

14.1 Adverse Event Summaries

All AEs will be coded using the MedDRA Version 21.1. A Treatment-emergent adverse event (TEAE) is defined as any event that has an onset date on or after the first dose of IP. All AEs collected in the eCRFs will be presented in data listings, but only TEAEs will be summarized in data tables. An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as (for ocular and non-ocular separately, where appropriate):

- Ocular TEAEs
- Non-ocular TEAEs
- [redacted]
- [redacted]
- [redacted]
- All SAEs
- [redacted]
- [redacted]
- TEAEs leading to study discontinuation
- TEAEs by Maximum Severity

Separate summaries (for ocular and non-ocular, where appropriate) will also be provided for these categories of TEAEs by SOC and PT. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

All AEs will be presented in a subject listing, with ocular AEs listed separately from non-ocular AEs. All TEAEs leading to study discontinuation will be listed separately. In addition, all SAEs will be presented in a separate listing.

14.2 [redacted]

[redacted]

[redacted]

14.3 Slit-Lamp Biomicroscopy Examination

A slit lamp biomicroscopy examination of the eyelid, conjunctiva, cornea, anterior chamber, iris, and lens will be conducted on both eyes at all scheduled visits pre-treatment, and an end of visit slit lamp will also be completed at Visits 1, 3, and 4. Magnification will be consistent with the investigator's standard clinical practice. The subject will be seated for the examination. The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). A table will summarize the findings utilizing frequency counts and percentages for each treatment group at each time point and for each eye (study eye and fellow eye). Percentages will be based on the number of subjects in each treatment group with responses. A subject listing of the slit-lamp parameters will also be produced.

14.4 Conjunctival Redness Assessment

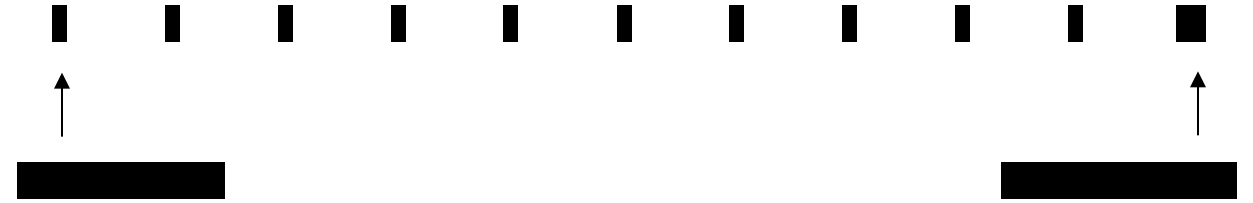
A conjunctival redness assessment is conducted at pre-treatment for all visits and at post-treatment for Visits 3 and 4 utilizing the [redacted] Redness Scale #6.0 Conjunctival Redness Assessments. The investigator will evaluate ocular redness of the three vessel beds (under the slit lamp) and grade according to the following scale:

[redacted]

14.5 IP Drop Comfort Assessment

[redacted]

[redacted]



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14.6 Intraocular Pressure

Intraocular pressure will be assessed via Goldmann applanation tonometry at Visits 1, 3, and 4. Results will be taken from a single measurement and will be recorded in mmHg. The IOP values and changes from baseline for each eye (study eye and fellow eye) will be summarized using continuous descriptive statistics by visit and eye for each treatment group. A subject listing of IOP results will also be produced.

15. Interim Analyses

An interim analysis has not been planned or performed for this study.

16. Changes from Protocol-Stated Analyses

As of the date of this SAP, the protocol-stated analyses have not been changed.

17. References

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

Kenward MG and Roger JH (1997), “Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood,” Biometrics, 53, 983–997. DOI: 10.2307/2533558

[redacted]

18. Revision History

Documentation of revision to the SAP will commence after the approval of Version 0.1.

19. Tables

Tables that will be included in the topline delivery are shown in boldface italics.

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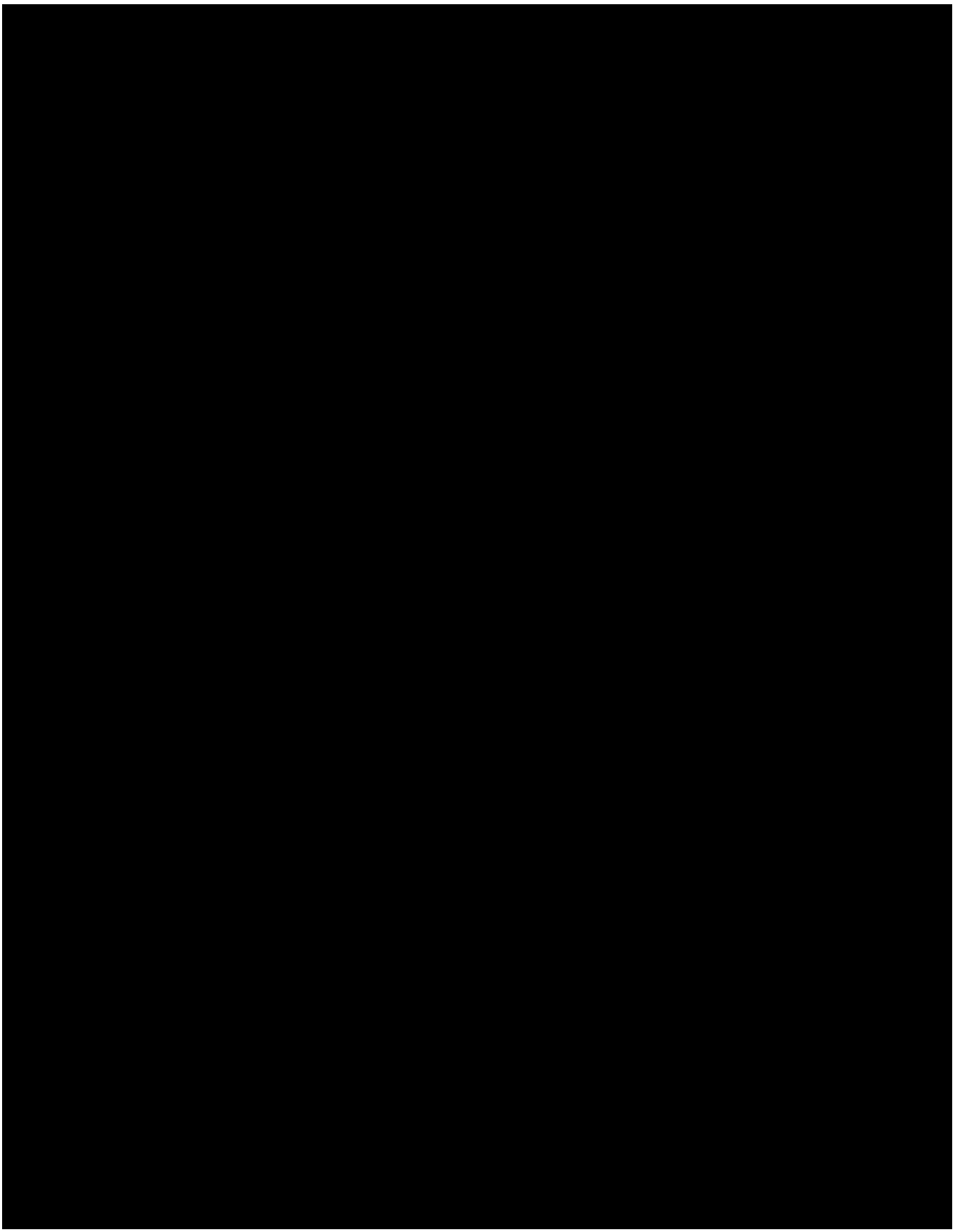

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21. Figures

Figures may be produced at the discretion of the study sponsor.