STATISTICAL ANALYSIS PLAN (SAP)

A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-2 study: Near Eye-vision Acuity Restoration)

Sponsor: Orasis Pharmaceuticals, Ltd

Protocol Number: 20-150-0003 (Phase 3)

Author: [redacted]

Date: 24FEB2022

Version: 2.0

A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia (the NEAR-2 study: Near Eye-vision Acuity Restoration)

Protocol Number: 20-150-0003 (Phase 3)

SAP Date: 24FEB2022

SAP Version: 2.0

SAP Preparation, Review, and Approvals

[redacted]

Table of Contents

List of Abbreviations 5
1. Introduction 6
2. Study Objectives 6
2.1 Study Variables 6
2.2 Primary Efficacy Endpoint 7
2.3 Secondary Efficacy Endpoints 7
2.3.1 Key Secondary Efficacy Endpoints 7
2.3.2 Other Secondary Efficacy Endpoints 7
2.4 Exploratory Efficacy Endpoints 8
2.5 Safety Endpoints 9
2.6 Statistical Hypotheses 9
3. Study Design and Procedures 15
3.1 Overall Study Design 15
3.2 Schedule of Visits and Measurements 18
4. Study Treatments 21
4.1 Method of Assigning Subjects to Treatment Groups 22
4.2 Masking and Unmasking 22
5. Sample Size and Power Considerations 22
6. Data Preparation 23
7. Analysis Sets 24
7.1 Full Analysis Set 24
7.2 Per Protocol Set 24
7.3 Safety Set 24
8. General Statistical Considerations 24
8.1 Unit of Analysis 24
8.2 Missing Data Handling and Sensitivity Analysis 24
8.3 Definition of Baseline 25
8.4 Data Analysis Conventions 25
8.5 Adjustment for Multiplicity 26
9. Disposition of Subjects 27
10. Demographic and Baseline Characteristics 27
10.1 Demographics 27
10.2 Baseline Characteristics 28
11. Medical History and Concomitant Medications 28
11.1 Medical History 28

11.2 Prior and Concomitant Medications 28
12. Efficacy Analyses 29
12.1 Primary and Key Secondary Efficacy Analysis 29
12.2 Sensitivity Analysis for Primary and Key Secondary Efficacy Endpoints 30
[redacted]
14. Safety Analyses 33
14.1 Adverse Event Summaries....33
14.2 Best Distance-Corrected Visual Acuity 34
[redacted]
15. Interim Analyses....36
16. Changes from Protocol-Stated Analyses 36
17. References 37
18. Revision History 37
19. Tables....39
20. Listings 42
21. Figures 43

List of Tables:

[redacted]

List of Figures:

Figure 1. Study Design.... 17

List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BDCVA	Best Distance-Corrected Visual Acuity
BID	Twice Daily
CI	Confidence Interval
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
GEE	Generalized Estimating Equation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMDF	Imputing Missing Data as Failures
IOP	Intraocular Pressure
IP	Investigational Product
IRT	Interactive Response Technology
HIPAA	Health Information Portability and Accountability Act
LDPE	Low-Density Polyethylene
LL-BDCVA	Low-Luminance Best Distance-Corrected Visual Acuity
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Square
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Not Clinically Significant
ODO	Observed Data Only
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TPA	Tipping Point Analysis
VA	Visual Acuity
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for the Orasis 20-150-0003 protocol, Version 2.0 (Amendment 1), dated 07Jan2021 (NEAR-2 study).

This Version 2.0 SAP replaces the previous finalized and signed Version 1.0 SAP, dated 22Nov2021.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Council for 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 (0.4% pilocarpine hydrochloride ophthalmic solution) for the temporary correction of presbyopia.

The secondary objectives of this study are to evaluate the safety and tolerability of CSF-1 versus Vehicle.

2.1 Study Variables

For all study variables, baseline is defined as the pre-treatment measurement taken at Visit 2 (Day 1). If the measurement is not available from Visit 2 (Day 1), then the measurement from Visit 1 (Day -14 to -1) 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 best distance-corrected visual acuity (BDCVA) at 40 cm (Precision Vision Chart) and BDCVA at 4 m (Early Treatment of Diabetic Retinopathy Study [ETDRS] chart), [redacted].

Safety variables include BDCVA at distance under normal and low-luminance testing conditions, slit-lamp biomicroscopy measures, conjunctival redness grading, and study drug drop comfort assessment, as well as intraocular pressure (IOP), dilated indirect fundoscopy, and adverse events (AEs). 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 -14 to -1). Further details regarding the procedures for conducting manifest refraction can be found in the BCVA protocol.

2.2 Primary Efficacy Endpoint

Percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in BDCVA at 40 cm (Precision Vision chart) and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) in the study eye at Visit 3 (Day 8), following Dose 1, 1 hour post-treatment.

2.3 Secondary Efficacy Endpoints

2.3.1 KEY SECONDARY EFFICACY ENDPOINTS

Key secondary efficacy endpoints include the following:

Percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in BDCVA at 40 cm (Precision Vision chart) and no loss in BDCVA ≥ 5 letters (ETDRS chart at 4 m) in the study eye at the following Visits, Doses and timepoints:

Visit 3 (Day 8)

Dose 1

- 2 hours following Dose 1

Dose 2

- 1 hour following Dose 2
- 2 hours following Dose 2

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

2.5 Safety Endpoints

The safety endpoints include the following:

- BDCVA (normal and low luminance) at 4 m
- Slit-lamp biomicroscopy
- Conjunctival redness grading
- Study drug drop comfort assessment
- IOP
- Dilated indirect fundoscopy
- AEs (reported, elicited, and observed)

2.6 Statistical Hypotheses

The primary efficacy hypothesis is:

H_{01}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 1 hour post-dose 1 = 0

H_{11}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 1 hour post-dose 1 ≠ 0

The study will be considered a success if the null hypothesis, H_{01}, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, H_{11}, tested as delineated in the primary efficacy analysis section, and the following secondary efficacy hypotheses will each be tested as stated under adjustments for multiplicity.

The key secondary efficacy hypotheses are:

Visit 3 (Day 8)

Visit 3, 2 Hours Post-Dose 1

H_{02}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 2 hours post-dose 1 = 0.

H_{12}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 2 hours post-dose 1 ≠ 0.

Visit 3, 1 Hour Post-Dose 2

H_{03}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 1 hour post-dose 2 = 0.

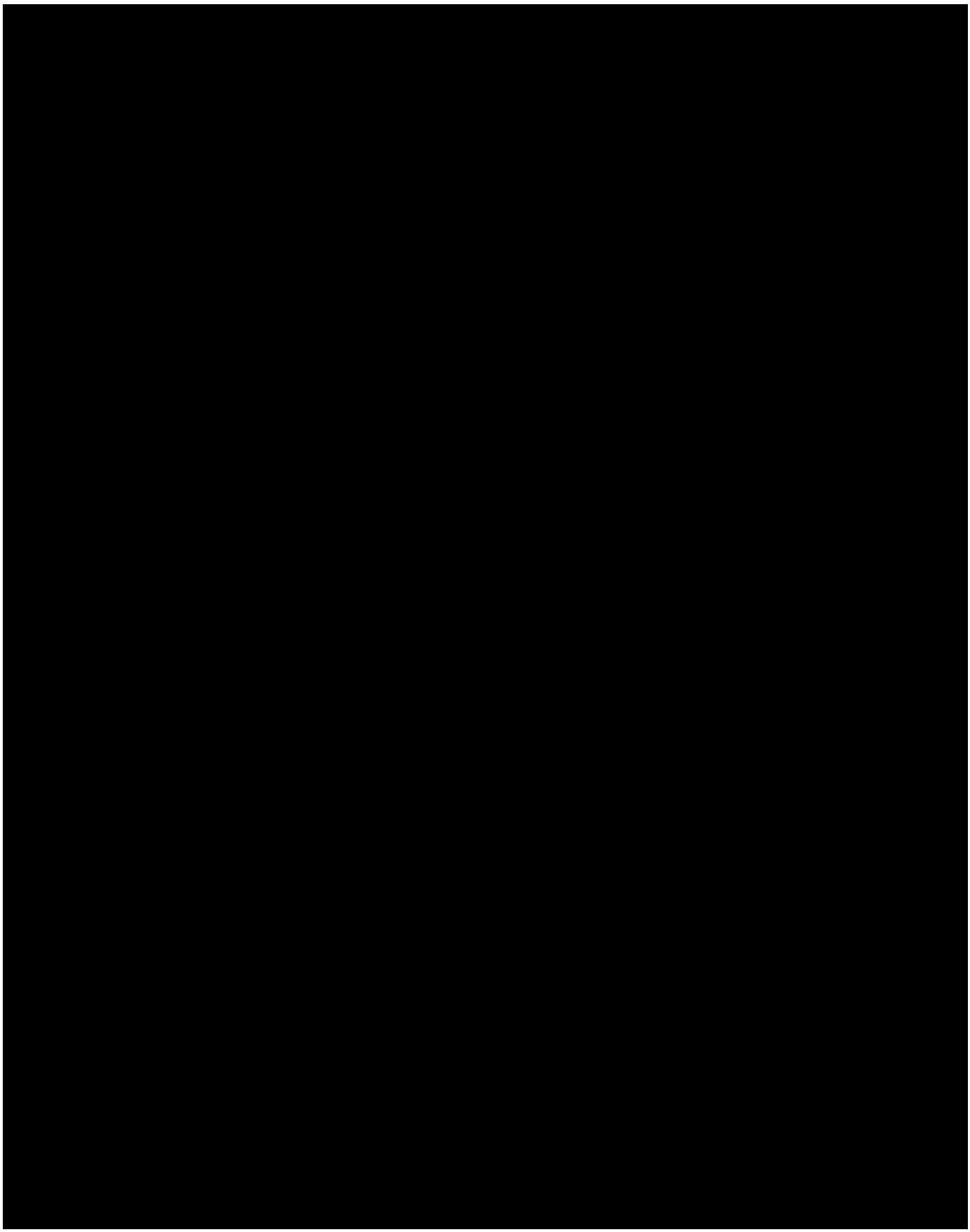
H_{13}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 1 hour post-dose 2 ≠ 0.

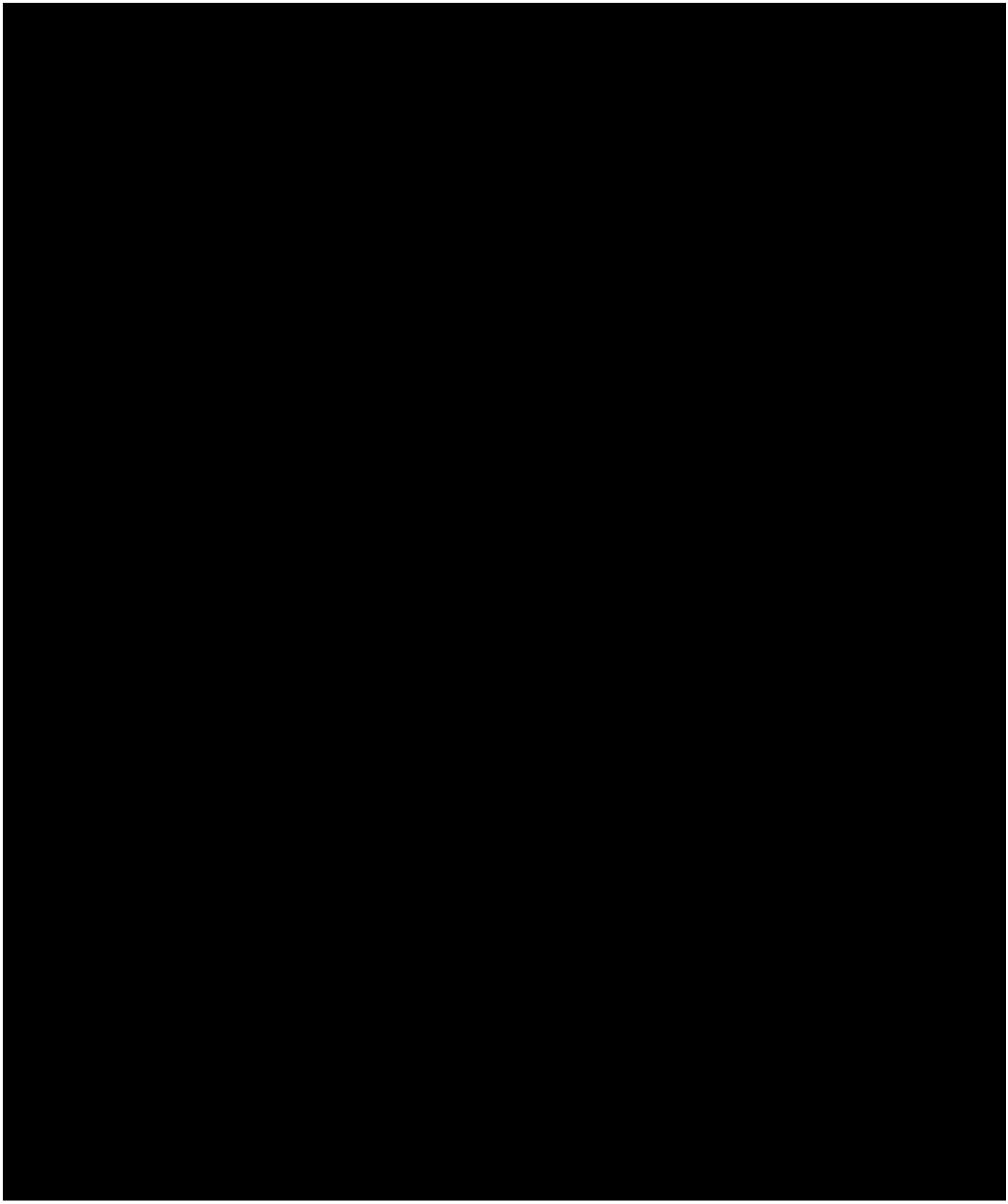
Visit 3, 2 Hours Post-Dose 2

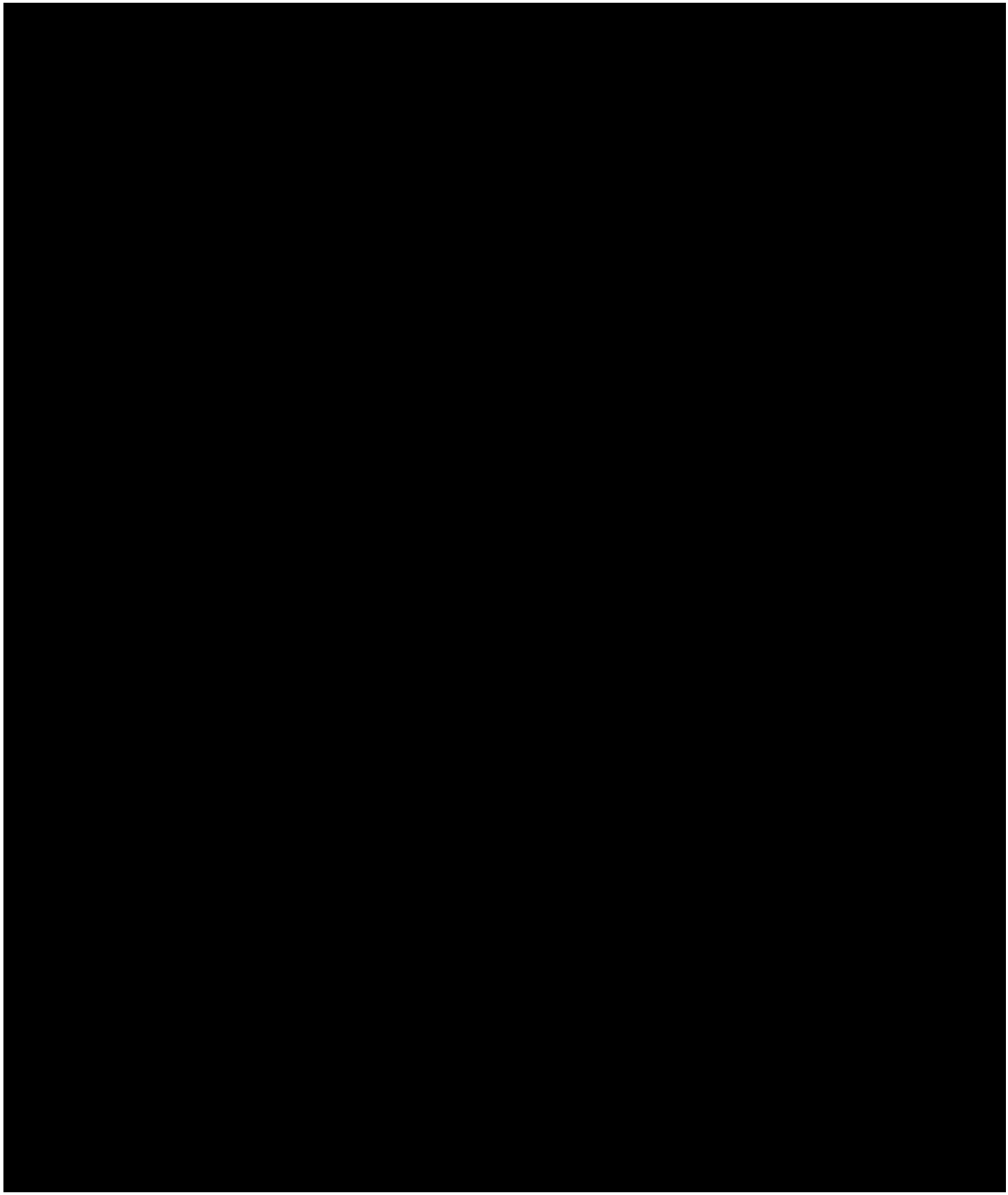
H_{04}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 2 hours post-dose 2 = 0.

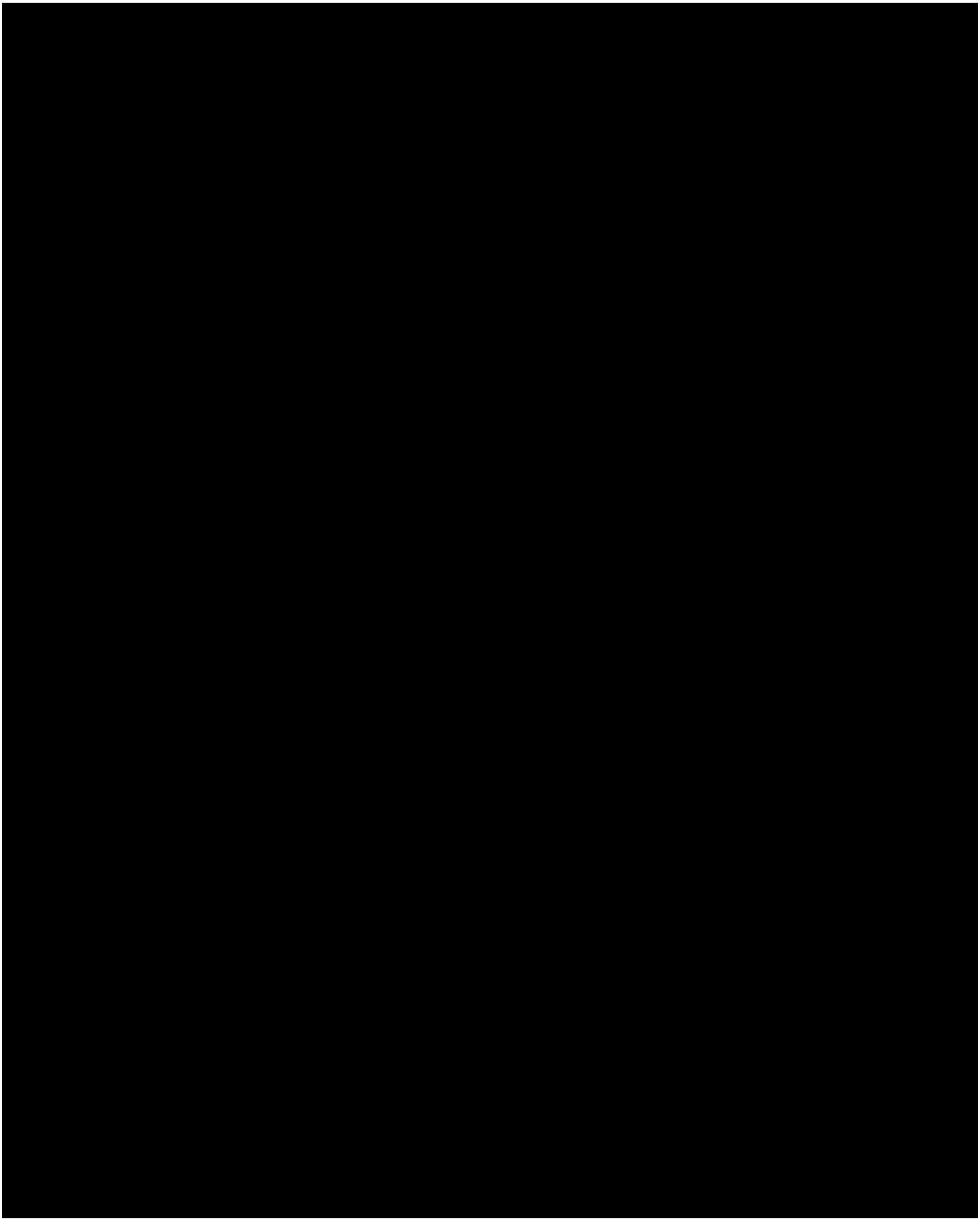
H_{14}: The difference between study eyes treated with CSF-1 and study eyes treated with Vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BDCVA at 40 cm (Precision Vision chart) without a loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) at Visit 3 (Day 8), 2 hours post-dose 2 ≠ 0.

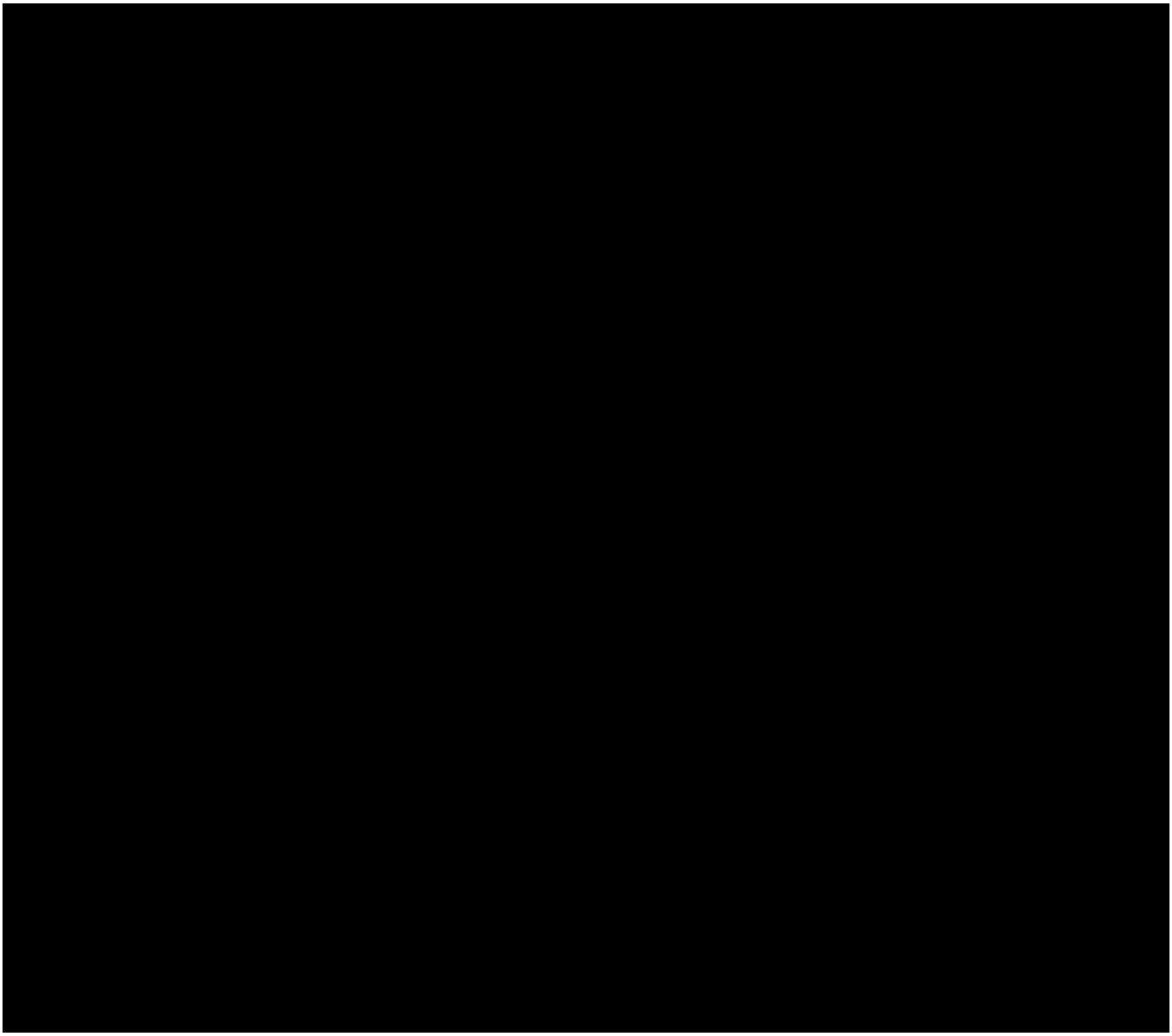
[redacted]











3. Study Design and Procedures

3.1 Overall Study Design

This is a four-visit multi-center, randomized, double-masked, parallel-group study evaluating the safety and efficacy of CSF-1 compared with Vehicle in approximately 300 subjects with presbyopia. The study design is summarized in Figure 1.

Visit 1 (Screening, Day -14 to -1): Qualified subjects will receive 1 drop of Vehicle instilled in each eye, followed by preliminary efficacy assessments to identify Vehicle responders at 15 minutes post-vehicle instillation.

Vehicle responder is defined as a subject who had a > 0.14 LogMAR (i.e., 7 letters) improvement in post-Vehicle treatment (at 15 minutes post-Vehicle treatment) monocular BDCVA in either eye at 40 cm compared to Visit 1 pre-treatment, or a > 0.14 LogMAR (i.e., 7 letters) improvement in monocular BDCVA in either eye at 40 cm between Visit 1 (pre-treatment) and Visit 2 (pre-treatment baseline).

Visit 2 (Day 1): Baseline assessments. Subjects who meet all inclusion and none of the exclusion criteria and qualify as Vehicle non-responders, will be randomized 1:1 to one of the following treatment arms:

- CSF-1 (0.4% pilocarpine hydrochloride ophthalmic solution)
- Vehicle

Pre-treatment measurements taken at this visit are considered as baseline.

At the Visit 2 (Day 1) clinic visit, study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 1. Dose 2 will be instilled by study personnel at 10:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 4 hours following Dose 2.

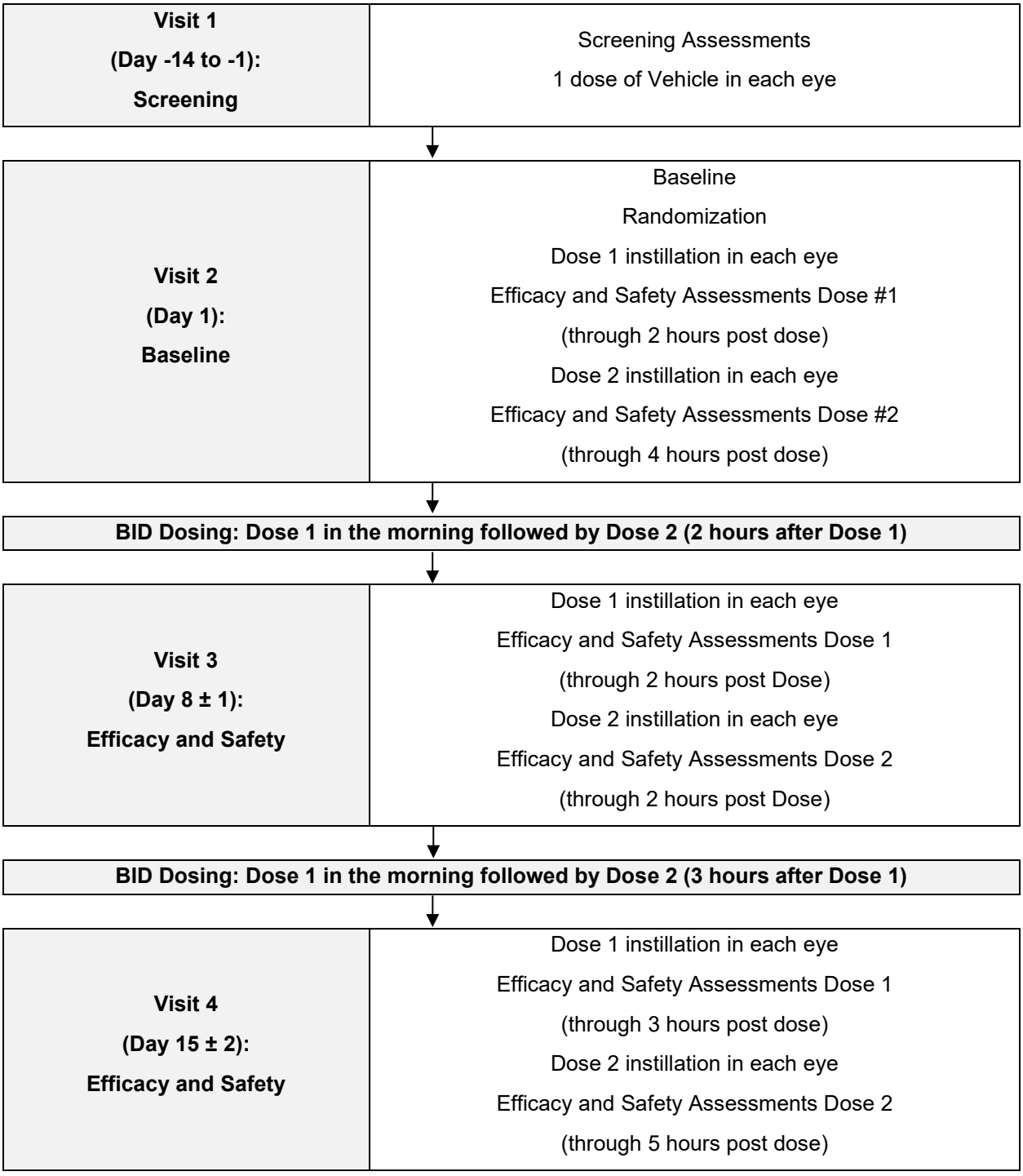
All subjects will be instructed to dose twice daily (BID) with a single drop in each eye for approximately 1 week. The first daily dose should occur in the morning, with the second dose following 2 hours later (±1 hour). Subjects will be instructed not to dose at home on clinic visit days.

Visit 3 (Day 8): Study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 1. Dose 2 will be instilled by study personnel at 10:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 2 hours following Dose 2.

All subjects will be instructed to dose twice daily (BID) with a single drop in each eye, for approximately 1 week. The first daily dose should occur in the morning with the second dose following 3 hours later (±1 hour). Subjects will be instructed not to dose at home on clinic visit days.

Visit 4 (Day 15): Study personnel will instill Dose 1 of study drug at 8:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted up to 3 hours following Dose 1. Dose 2 will be instilled by study personnel at 11:30 AM ± 30 minutes in each eye. Efficacy and safety assessments will be conducted for 5 hours following Dose 2.

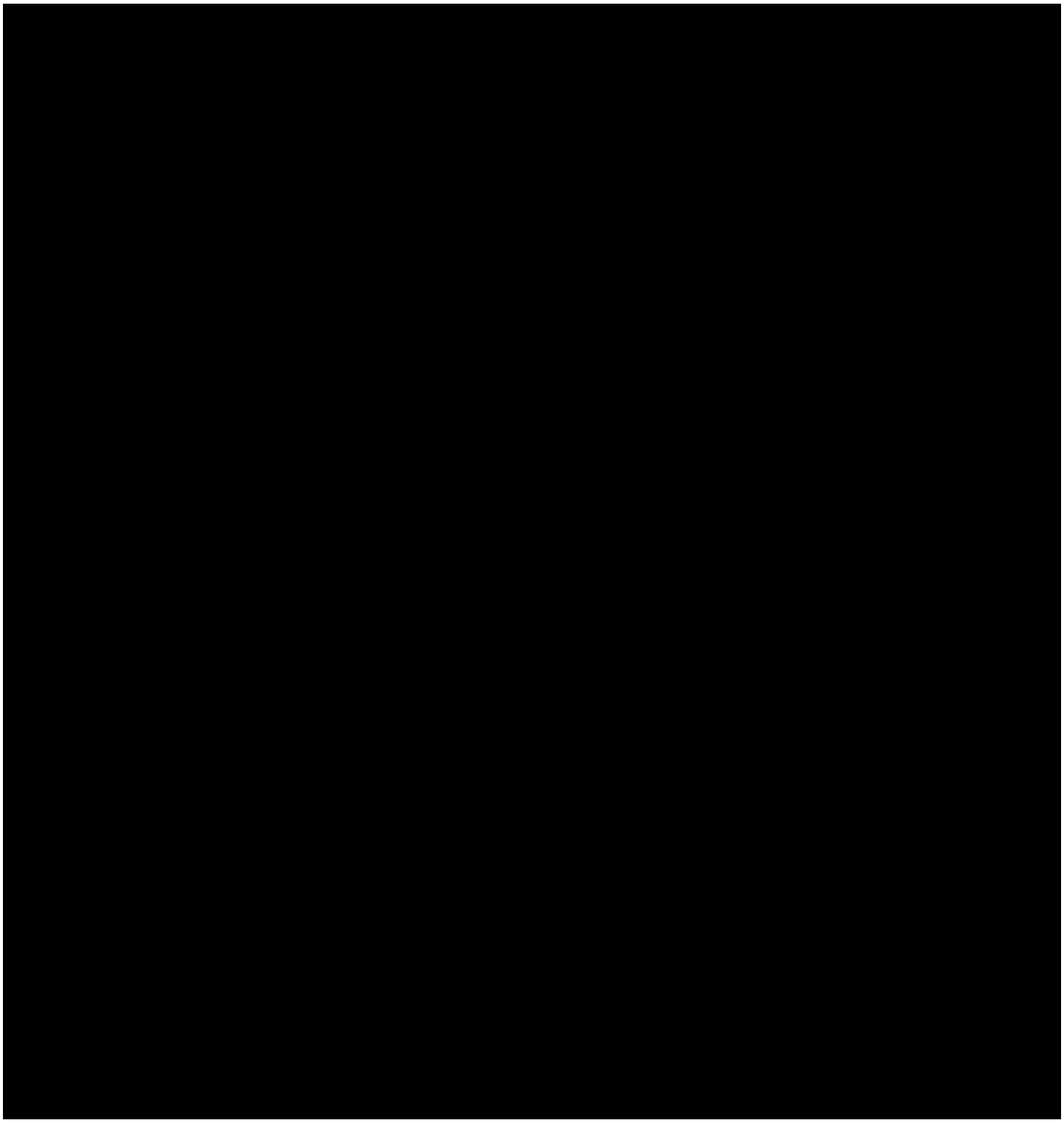
Figure 1. Study Design

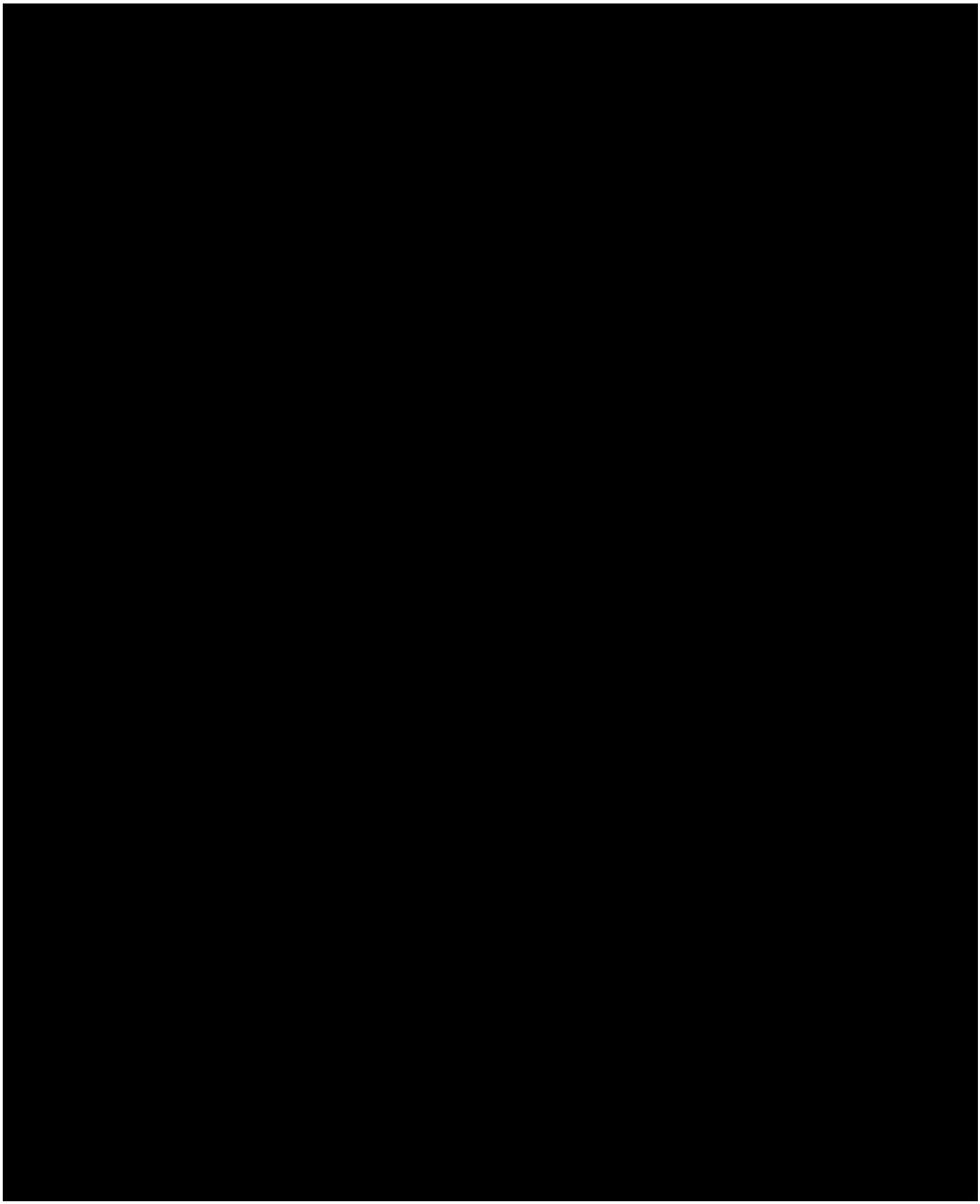


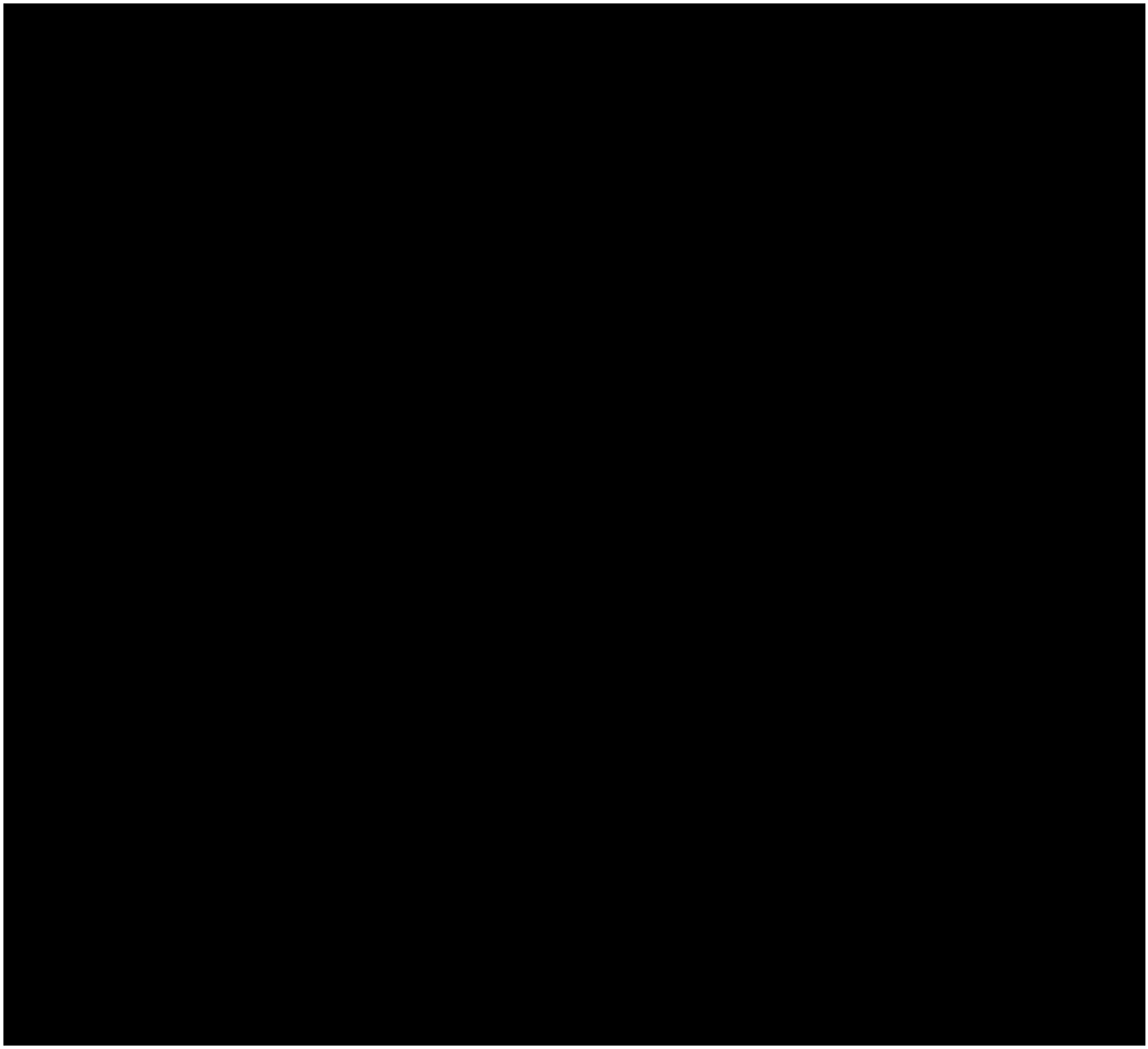
3.2 Schedule of Visits and Measurements

The schedule of visits and assessments is provided in Table 1.

Table 1 Schedule of Visits and Assessments







4. Study Treatments

The investigational product (IP) is CSF-1, a sterile topical eye drop solution. The formulation developed by Orasis Pharmaceuticals Ltd. is a preservative-free eye drop, containing the active ingredient pilocarpine hydrochloride 0.4%, with the addition of standard pharmacopoeial excipients used in sterile ophthalmic solutions.

The vehicle (CSF-1 placebo) is a topical eye drop solution containing the same ingredients as in CSF-1 except for the active ingredient.

Both IP and Vehicle are packaged in a single-dose transparent low-density polyethylene (LDPE) vials, enclosed within a pouch. Each pouch includes five vials. Kits will be dispensed to subjects at Visit 2 (Day 1) and Visit 3 (Day 8) with 1 week of at-home dosing in each kit. CSF-1 will be evaluated for comparison to Vehicle.

Following the pre-treatment assessments, qualified subjects will be randomized to 1:1 to one of the following treatment arms:

1. CSF-1: Pilocarpine Hydrochloride (0.4%) Ophthalmic Solution
2. Placebo (Vehicle)

After randomization at Visit 2 (Day 1), subjects will receive study drug and a paper dosing diary. Each subject will instill one drop of study drug to each eye and keep aside the used vial to be returned to the site

at next visit for compliance check. Following Visit 2, subjects will be instructed to dose bilaterally BID (with 2 hours (+1 hour) between doses) and record doses in their diary until Visit 3. Subjects should not dose at home on day of Visit 3. Following Visit 3, after subjects receive their study drug and dosing diary, subjects will be instructed to dose bilaterally BID (with 3 hours (+1 hour) between doses) and record doses in their diary until Visit 4. Subjects should not dose at home on day of Visit 4. At Visit 4, subjects will receive their doses at the visit by study personnel after the required pre-treatment assessments and their study drug will be collected. Subjects will exit the study after all assessments are complete at Visit 4.

4.1 Method of Assigning Subjects to Treatment Groups

Each subject who signs an informed consent form (ICF) will be assigned a subject number. Subject numbers will be assigned in sequential order beginning with 001. Once a subject meets all qualification criteria at Visit 2 (Day 1), they will be randomized in a 1:1 ratio via an Interactive Response Technology (IRT) system to one of the following treatment groups: (1) CSF-1 or (2) Vehicle, and stratified by iris color (brown versus light [i.e., blue, green, gray, and hazel]) and by baseline manifest refraction spherical equivalent <-0.5 D, -0.5 D to +0.75 D, and >+0.75 D); randomization will not be stratified by site.

At least, approximately, 30% of subjects will have a light iris and at least, approximately, 30% will have a brown iris. The actual percentages will vary based on enrollment.

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., iris color and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.

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), [redacted] 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

A total sample size of 280 subjects (140 subjects per arm) yields > 97.5% power to establish superiority of CSF-1 to Vehicle in the percentage of study eyes demonstrating a ≥ 3-line (15-letter) gain from baseline in BDCVA at 40 cm (Precision Vision chart) and no loss of BDCVA ≥ 5 letters (ETDRS at 4 m), 1-hour post

each dose on Visit 3 (Day 8) assuming a response rate of 42.5% in CSF-1 and 17.5% in Vehicle using a Pearson chi-squared test with a 2-sided significance level of 0.05.

[redacted]

Accounting for approximately a 5% discontinuation rate, approximately 150 subjects per arm (approximately 300 total) will be randomized.

6. Data Preparation

All reported study data will be recorded on the eCRFs supplied by [redacted] using iMedNet™. 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 [redacted] Inc. in consultation with SDC.

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 SDC 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 SDC and sponsor personnel.

- Protocol deviations have been identified and status defined (major/minor deviations), and completed prior to database lock and study unmasking.
- Analysis populations have been determined, and completed prior to database lock and study unmasking.
- Randomized treatment codes have been unmasked.

7. Analysis Sets

7.1 Full Analysis Set

The full analysis set (FAS) will include all randomized subjects who have received at least one dose of the study drug. Subjects in the FAS will be analyzed as randomized. The FAS analysis set will be the primary analysis set for the determination of efficacy.

7.2 Per Protocol Set

The per-protocol set (PPS) will include subjects in the FAS who do not have significant protocol deviations that affect the primary efficacy endpoint analyses. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PPS will be analyzed as treated. The PPS analysis will be supportive of the primary and key secondary efficacy analysis performed with FAS.

7.3 Safety Set

The safety set (SAF) will include all subjects who have received at least one dose of the study drug. Subjects in the SAF 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 endpoints.

The study eye will be defined by the study Investigator as the eye that meets all enrollment criteria. If both eyes meet all enrollment criteria, then the eye with the worse Visit 2 pre-treatment/baseline BDCVA at 40 cm (Precision Vision chart) will be the study eye. If both eyes have the same BDCVA at 40 cm, the right eye will be the study eye.

8.2 Missing Data Handling and Sensitivity Analysis

The primary efficacy analysis and the key secondary analyses will be performed on the FAS, as described in section 12.1. In the event of missing data, the primary imputation method will be Multiple Imputation (MI), using randomized treatment-based Markov Chain Monte Carlo (MCMC). Sensitivity analyses will also be performed on the primary and key secondary efficacy endpoints measured at Visit 3 (Day 8). These sensitivity analyses will be considered supportive of the primary and key secondary analyses.

8.3 Definition of Baseline

For all endpoints, 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 Visit 1 (Day -14 to -1) will be used as baseline. Change from baseline will be calculated as: Post-Baseline Measure – Baseline Measure.

8.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. 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 (SD), 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 post-baseline visit (Post-Baseline Visit – Baseline Visit), with baseline defined in Section 8.3 of this SAP.

Gains or improvements in BDCVA at 40 cm (Precision Vision chart) of ≥ 3-lines (15-letters) are defined as changes from baseline in BDCVA at 40 cm (Precision Vision chart) of ≤ -0.30 logMAR (e.g., -0.30, -0.32, … logMAR).

Gains or improvements in BDCVA at 40 cm (Precision Vision chart) of ≥ 2-line (10-letters) are defined as changes from baseline in BDCVA at 40 cm (Precision Vision chart) of ≤ -0.20 logMAR (e.g., -0.20, -0.22, … logMAR).

Similarly, loss in BDCVA of ≥ 5 letters (ETDRS at 4 m) are defined as changes from baseline in BDCVA (ETDRS at 4 m) of ≥ 0.10 logMAR (e.g., 0.10, 0.12, … logMAR).

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.

8.5 Adjustment for Multiplicity

If the primary null hypothesis, H_{01}, is rejected at a 2-sided alpha = 0.05 in favor of CSF-1 in the alternative hypothesis, H_{11}, tested as delineated in the primary efficacy analysis section (Section 12.1), then the study will be considered a success and the following key secondary hypotheses will be tested in hierarchical order, each at a 2-sided alpha = 0.05, where inference will be made on each null hypothesis only if the prior null hypotheses are rejected in favor of CSF-1.

1. Visit 3 (Day 8), 2 hours following Dose 1 (H_{02})
2. Visit 3 (Day 8), 1 hour following Dose 2 (H_{03})
3. Visit 3 (Day 8), 2 hours following Dose 2 (H_{04})

[redacted]

[redacted]

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 4 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, death, 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 (FAS, PPS, and SAF) will be displayed by treatment arm, with the number of subjects and percentages calculated using randomized subjects as the denominator. The number and percentage of subjects with any (major, or minor) protocol deviations 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 PPS. There will also be a listing of screen failures.

10. Demographic and Baseline Characteristics

10.1 Demographics

Subject demographic data collected in this study, age, sex, race, ethnicity, and childbearing potential. 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 (study eye) will be classified as heterochromia. Sex, race, ethnicity, childbearing potential, and iris color will be presented using descriptive summary statistics with frequency counts and percentages. Age (years) will be summarized with continuous descriptive statistics. Categorical variables will be summarized with number and percentage

Demographic variables along with two baseline characteristics, iris color of study eye and manifest refraction spherical equivalent (MRSE), will be summarized for the FAS and PPS by treatment arm and overall in tables. A subject listing that includes all summarized demographic and baseline 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 -14 to -1). Subject level listings will be used to present pre-treatment information from the FAS at the eye level when appropriate. Baseline characteristics will be contained in subject listings only and will include:

- Manifest refraction
- Iris color
- 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 23.0. 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 SAF. 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. All SOC and PTs within an SOC category will be ordered by descending frequency based on all subjects.

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 March 2020) 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 (e.g., multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification of “Uncoded,” but the missing preferred term will be replaced by the verbatim term entered in the eCRF.

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 (Day -14 to -1). Prior and concomitant medications will be summarized using the SAF. 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. The ATC Classes and preferred names within an ATC Class will be ordered by descending frequency based on all subjects.

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

12. Efficacy Analyses

The primary efficacy and key secondary efficacy analyses are described in Section 12.1. Sensitivity analyses on the primary and key secondary efficacy endpoints are described in Section 12.2. and will be performed using the FAS.

[redacted]

12.1 Primary and Key Secondary Efficacy Analysis

The primary efficacy endpoint in this study is the percentage of subjects with a ≥ 3-line (15-letter) gain, from baseline, in best distance-corrected visual acuity (BDCVA) at 40 cm (Precision Vision chart) and no loss in BDCVA ≥ 5 letters (ETDRS chart) at Visit 3, 1 hour following Dose 1 in the study eye. The key secondary efficacy endpoints are defined the same as the primary efficacy endpoint, except for being measured at 2 hours following Dose 1, 1 hour following Dose 2, and 2 hours following Dose 2, all at Visit 3.

The primary and key secondary efficacy analysis will be conducted in the FAS with missing data handled in the following manners:

1. Discontinuation of study drug and non-optimal compliance will be ignored [treatment policy strategy].
2. Withdrawal due to lack of efficacy or AEs: missing data will be singly imputed as failure [hypothetical strategy].
3. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methods.

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

Variables for treatment group, baseline for BDCVA at 40 cm and baseline for BDCVA at 4 m will also be included in the multiple imputation model. 25 complete imputed datasets will be created.

Example SAS® code for the multiple imputation:

```
PROC MI DATA=DATAIN OUT=MI NIMPUTE=25 SEED=118787 minimum=-0.3 maximum=1;
          MCMC INITIAL=EM;
          VAR TRTPN VA40 VA40BL VA4 VA4BL;
RUN;
```

Where TRTPN = treatment group, coded 1 for CSF-1, else 0

VA40 = value of BDCVA at 40 cm for Visit 3, 1 hour after Dose 1

VA40BL = baseline value of BDCVA at 40 cm

VA4 = value of BDCVA at 4 m for Visit 3, 1 hour after Dose 1

VA4BL = baseline value of BDCVA at 4 m

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

Example SAS® code for the logistic model is shown here:

```
PROC LOGISTIC DATA=MI DESCENDING OUTEST=PARMS COVOUT;
      BY _IMPUTATION_;
      CLASS TRTP;
      MODEL AVALC = BASE TRTP;
RUN;
```

where

- TRTP is the treatment arm (CSF-1, Vehicle);
- BASE is the baseline of BDCVA (letters) at 40 cm in the study eye;
- AVALC is the indicator for efficacy variable (Y, N).

SAS® PROC MIANALYZE will be used to obtain the overall p-value, odds ratio, and 95% confidence interval (CI) for odds ratio.

12.2 Sensitivity Analysis for Primary and Key Secondary Efficacy Endpoints

Sensitivity Analysis for the primary and key secondary efficacy endpoints include:

1. All missing data imputed as failure using the FAS
2. Observed data only using the FAS

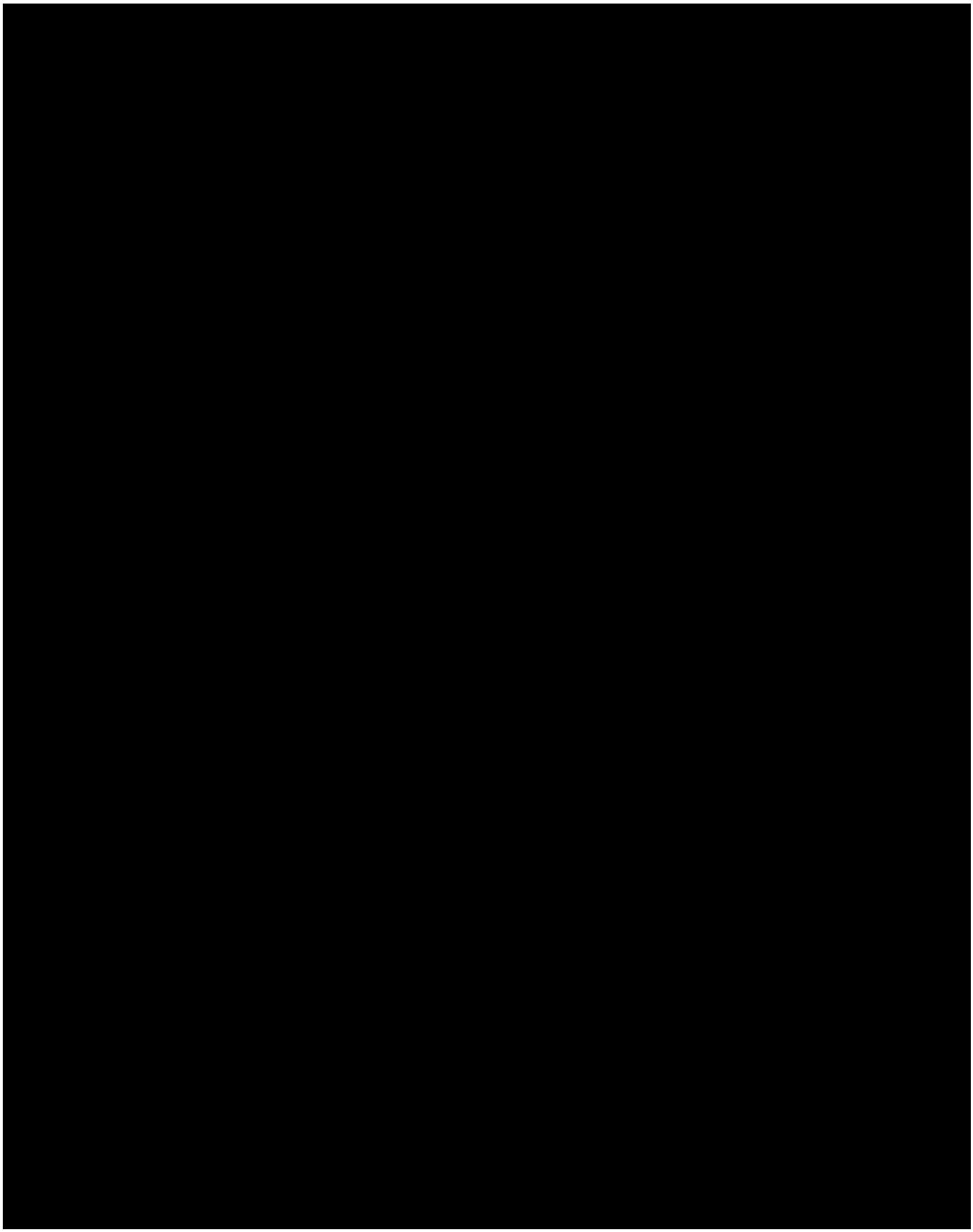
3. Observed data only using the PPS
4. Missing data will be imputed employing tipping point approach. The analysis will be based on the FAS

For #1, #2 and #3 sensitivity analyses, the analysis of primary and key secondary efficacy endpoints will be 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 95% confidence interval (CI) for odds ratio will be provided. p-values will be presented for the main effect of treatment group using a Wald statistic.

Tipping Point Analysis of Primary and Key Secondary Efficacy Variables

Missing primary and key secondary efficacy endpoint values (i.e., binary response values) will be imputed using tipping point approach. 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 will be 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% confidence interval (CI) for odds ratio will be provided. If the p-value is less or equal to 0.05 for the worst case, then stop there. If the p-value is greater than 0.05 for the worst case, then set the missing records as failures or successes in all possible combinations from worse case to the best case until the p-value turns from >0.05 to ≤ 0.05.

[redacted]



14. Safety Analyses

All safety analyses will be conducted using the SAF. In addition to AEs, BCVA at distance under normal and low-luminance testing conditions, findings from slit-lamp biomicroscopy examination, conjunctival redness grading, study drug drop comfort assessment, dilated indirect fundoscopy, and 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 23.0. A treatment-emergent adverse event (TEAE) is defined as any event that has an onset date on or after the first dose of study drug. 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
- Ocular Non-Serious TEAEs
- Non-ocular Non-Serious TEAEs
- Most Frequent (> 5% in any arm) Ocular TEAEs
- Most Frequent (> 5% in any arm) Non-ocular TEAEs
- Expected TEAEs
- Unexpected TEAEs
- Suspected treatment-related TEAEs
- All SAEs
- Suspected treatment-related SAEs
- Not Suspected treatment-related SAEs

- TEAEs leading to study discontinuation
- TEAEs by maximal severity
- Suspected Treatment-Related Ocular TEAEs by maximal severity
- Suspected Treatment-Related Non-ocular TEAEs by maximal severity
- Not Suspected Treatment-Related Ocular TEAEs by maximal severity
- Not Suspected Treatment-Related Non-ocular TEAEs by maximal 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 CSF-1 treated 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 Best Distance-Corrected Visual Acuity

Safety variables include BDCVA at 4 m under normal and low-luminance testing conditions.

Monocular BDCVA summaries will specify study eye and fellow eye. Monocular BDCVA and Low-Luminance BDCVA (LL-BDCVA) at 4 m will be measured at pre-treatment, post-Dose 1 and post-Dose 2 as mentioned in the schedule of assessments (Section 3.2). The observed BDCVA as well as the change from baseline in BDCVA and LL-BDCVA will be summarized by treatment group using continuous descriptive summary statistics, and subject-specific BDCVA and LL-BDCVA data will also be presented in a listing for each visual range, separately. Tables will also provide the number and percentage of eyes that lose 10 or more letters BCDVA at 4 m.

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 Visit 1 (Day -14 to -1), Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15). 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 with frequency counts and percentages for each treatment group at each timepoint 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

Pre-treatment ocular redness will be assessed using the [redacted] Scale #6 at Visit 1 (Day -14 to -1), Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15). Post-treatment ocular redness will be assessed at Visit 2 (Day 1), Visit 3 (Day 8) and Visit 4 (Day 15), at 20 minutes, 1 hour post-dose 1, and End of Visit. The [redacted] Scale #6 uses the following scoring system:

0 = None

1 = Mild: Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal

2 = Moderate: More apparent dilation of blood vessels; vessel color is more intense (redder); involves the majority of the vessel bed

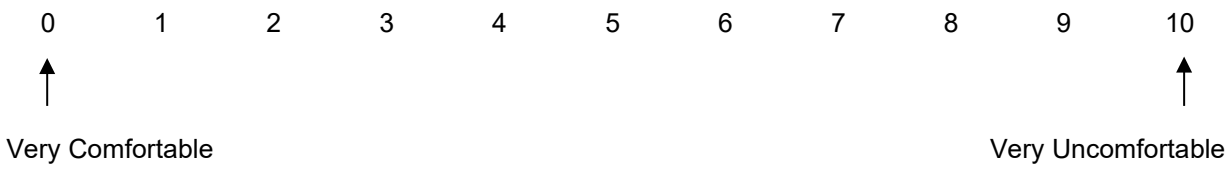
3 = Severe: Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red, may be less red or pink in presence of chemosis, is not quadrantic

4 = Extremely Severe: Large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed

Conjunctival redness grades and changes from baseline will be summarized by treatment group, for the study eye and fellow eye separately, using continuous descriptive summary statistics. At each post-treatment timepoint, proportions of subjects who are Grade 0 (None) and Grade ≤ 1.0 will be summarized by count and percentage. The results of the conjunctival redness assessments will also be presented in a subject listing.

14.5 Study Drug Drop Comfort Assessment

Study drug drop comfort will be assessed for each eye immediately upon instillation, 30 seconds, and at 1, 5, and 10 minutes post-treatment at Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15) using the [redacted] Drop Comfort Scale. Subjects will subjectively evaluate their own level of ocular comfort and score according to the following 0-10 scale:



Study drug drop comfort scores will be summarized by treatment group, for the study eye and fellow eye separately, using continuous descriptive summary statistics. At each post-treatment timepoint, the proportions of subjects whose scores are 0, ≤ 1, and ≤ 2 will be summarized by count and percentage. The [redacted] drop comfort assessments will also be presented in a subject listing.

14.6 Intraocular Pressure

Intraocular pressure will be assessed via Goldmann applanation tonometry at Visit 1 (Day -14 to -1), Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15). 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.

14.7 Dilated Indirect Fundoscopy

Dilated indirect fundoscopy will be performed at Visit 1 (Day -14 to -1) and Visit 4 (Day 15) using indirect ophthalmoscope. Dilated indirect fundoscopy should always be performed after IOP and all other ocular examinations.

Dilated Indirect fundoscopy parameters collected for the left and right eyes include, vitreous, retina, macula, choroid, and optic nerve. Each parameter is rated “Normal,” “Abnormal (NCS),” or “Abnormal (CS).” The subject listing of dilated indirect fundoscopy will include all ratings collected for each parameter in both eyes and the investigator’s findings associated with each parameter at each timepoint.

15. Interim Analyses

An interim analysis is not planned for this study.

16. Changes from Protocol-Stated Analyses

[redacted]

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)

18. Revision History

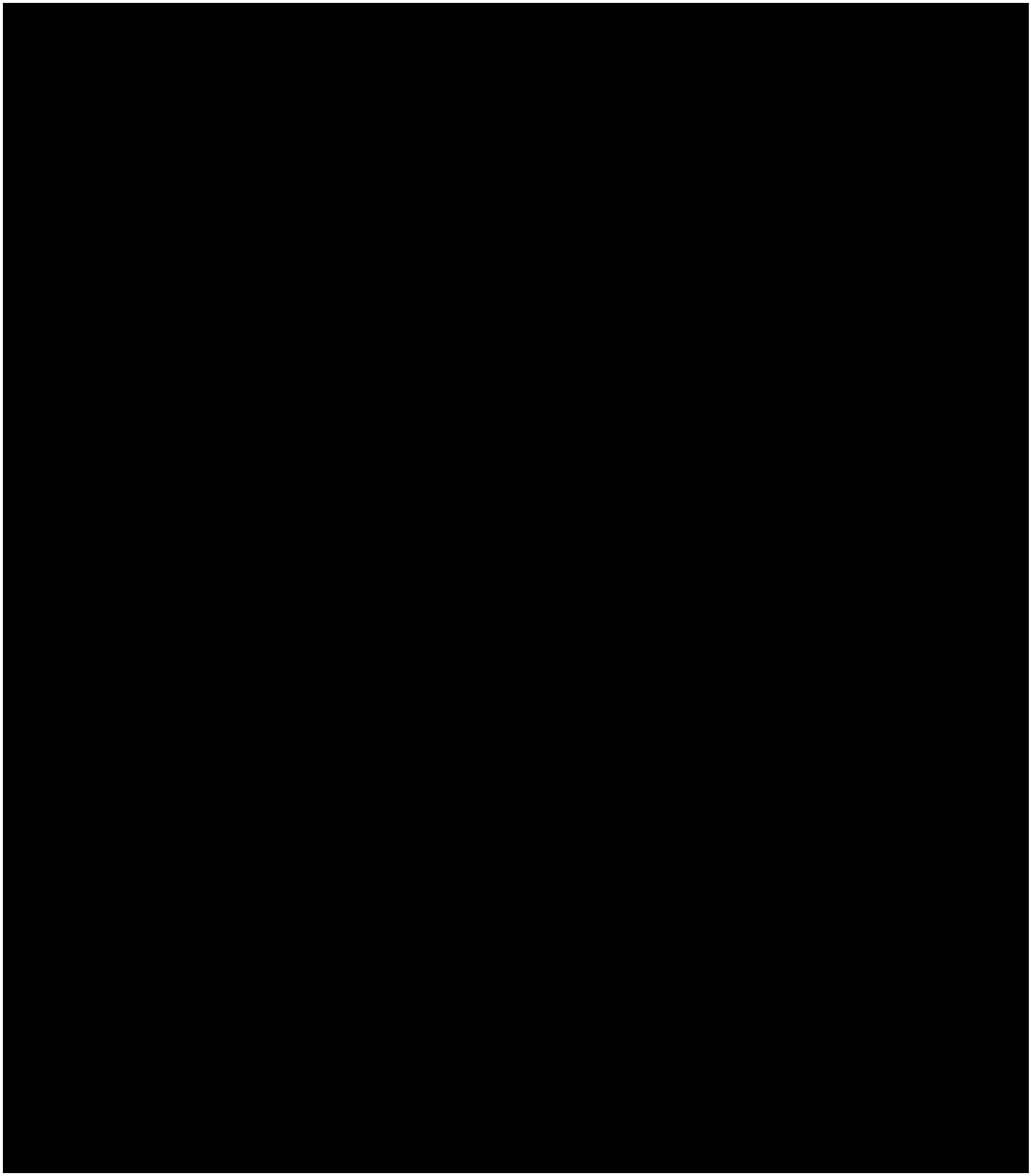
This SAP v2.0 amendment was issued following SAP v1.0, issued on 22NOV2021.

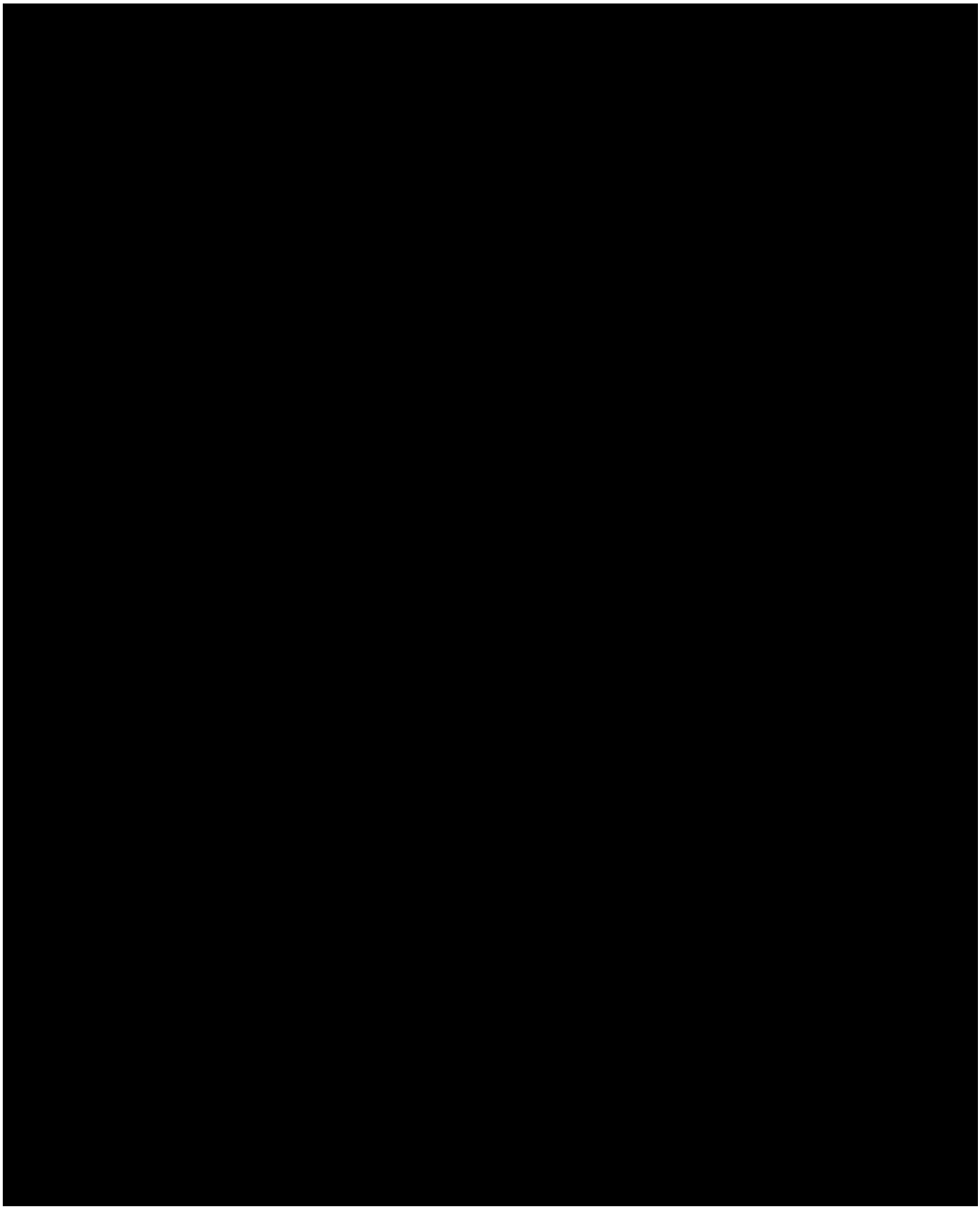
Table 2. Summary of Changes from SAP v. 1.0

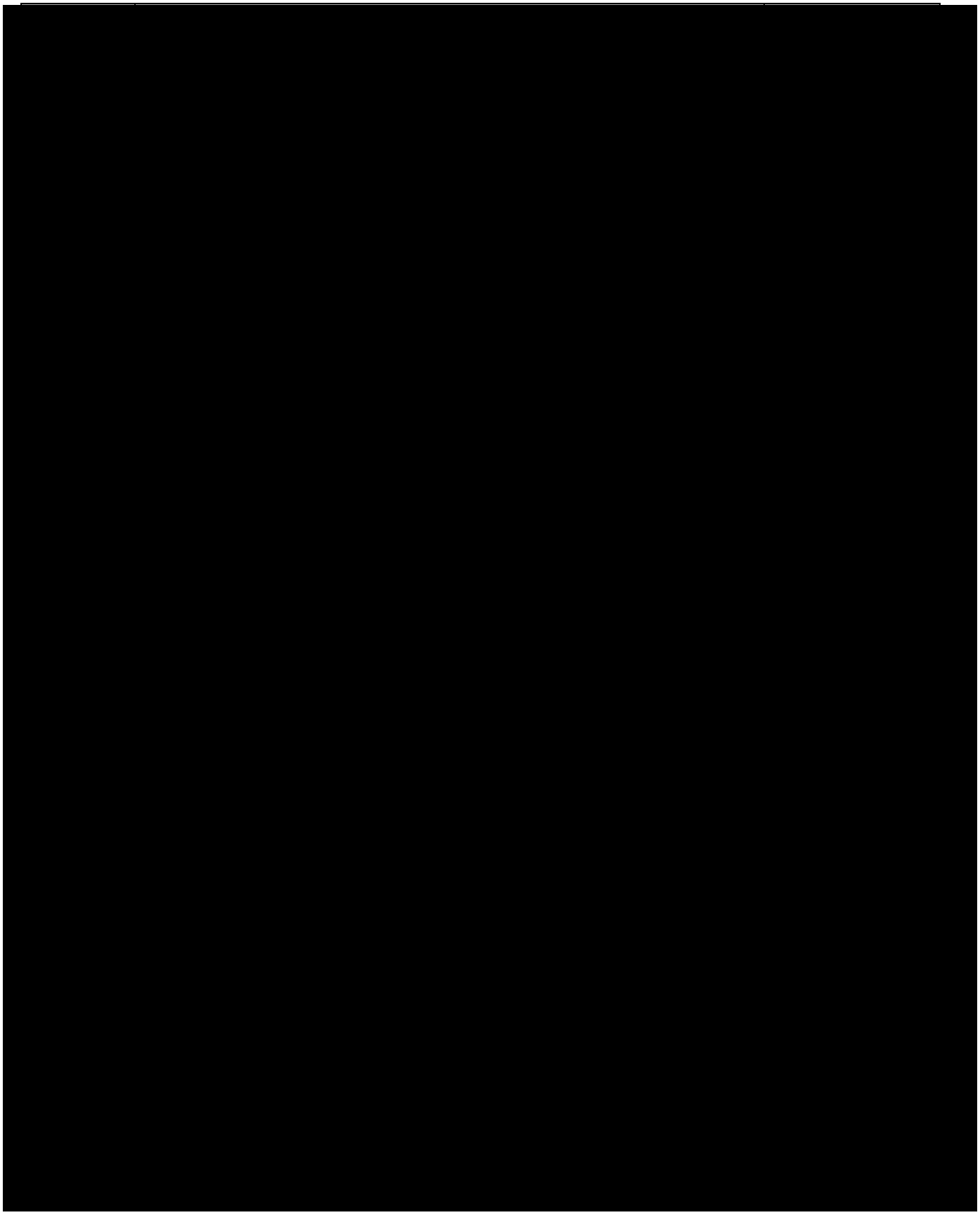
[redacted]

19. Tables

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







[redacted]

20. Listings

[redacted]

21. Figures

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