Protocol No./Title: A Multi-Center, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group, Study to Evaluate the Safety and Efficacy of CSB-001 Ophthalmic Solution 0.1% in Stage 2 and 3 Neurotrophic Keratitis Subjects

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STATISTICAL ANALYSIS PLAN

A Multi-Center, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of CSB-001 Ophthalmic Solution 0.1% in Stage 2 and 3 Neurotrophic Keratitis Subjects

Protocol Number: CSB-C20-003

Sponsor: Claris Biotherapeutics, Inc.

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Approval

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Revision History

Version and Date	Reason for Change	Comments
Version 1.0, 10 June 2024	Initial version	

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AS-OCT	anterior segment optical coherence tomography
VA	visual acuity
c-Met	mesenchymal epithelial transition factor (dHGF receptor)
CSB-001 0.1% or CSB-001	dHGF ophthalmic solution 0.1%
dHGF	5-amino acid deleted hepatocyte growth factor Also referred to as: hemopoietin, KP-100, HPO, SB-dHGF, KP-HGF-001, rhdHGF
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration (US)
g	gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HGF	hepatocyte growth factor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IT	intrathecal
IOP	intraocular pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-Treat
IUD	Intrauterine Device
IV	intravenous
kg	kilogram
Lesion size	Maximum diameter of defect in mm measured by the CRC
Lesion area	Area of defect measured by the CRC
LDPE BFS	low-density polyethylene blow-fill-seal

LOCF	Last Observation Carried Forward
LPS	lipopolysaccharides
MedDRA	Medical Dictionary for Regulatory Activities
mL	millimeter
NK	neurotrophic keratitis
OCT	Optical Coherence Tomography
PBS	phosphate buffered saline
PED	persistent epithelial defect
PI	Principal Investigator
QID	four times daily (approximately 4 hours apart during waking hours)
rhHGF	recombinant human hepatocyte growth factor
rhdHGF	recombinant human deleted hepatocyte growth factor
SAE	serious adverse event
SAP	Statistical Analysis Plan

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1.0 INTRODUCTION TO THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan (SAP) is based on protocol CSB-C20-003 'A Multi-center, Randomized, Double-masked, Vehicle-controlled, Parallel-group, Study to Evaluate the Safety and Efficacy of CSB-001 Ophthalmic Solution 0.1% in Stage 2 and 3 Neurotrophic Keratitis Subjects', Version 5.0, dated 21July2023. It details the methodology to be used in analyzing the data and outlines the specifications in the Tables, Figures and Listings (TFLs) for data to be included for executing the final statistical analyses for this study.

The analyses specified in this document supersede any high-level analysis plan described in the protocol.

2.0 INTRODUCTION TO THE STUDY

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to compare the safety and efficacy of CSB-001 0.1% to that of CSB-001 vehicle following QID dosing for 8 weeks in the study eye of subjects with stage 2 or 3 NK.

Safety will be assessed via adverse event reporting and standard ophthalmic assessments (including slit-lamp and dilated fundus examination, pinhole distance visual acuity, and intraocular pressure). Ocular tolerability will be assessed using a subject questionnaire administered by the site staff.

The primary efficacy endpoint is the proportion of subjects achieving complete corneal healing. Complete corneal healing is defined as absence of corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) at Week 8 and the absence of corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) two weeks later at Week 10 as assessed by a central reading center (CRC).

2.1.2 Other Objectives

Subjects randomized in the controlled phase to the vehicle arm whose cornea is not healed are eligible to receive an 8-week course of CSB-001 treatment (uncontrolled treatment phase). The objective is to accrue additional safety data for CSB-001 in eyes with NK.

2.2 Study Endpoints

For the primary efficacy endpoint, complete corneal healing is defined as absence of corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) at Week 8 and the absence of the

corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) two weeks later at Week 10 as assessed by a central reading center.

For the secondary endpoints, cornea healing is defined as absence of corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) at any single timepoint.

2.2.1 Primary Efficacy Endpoint and Estimand

The primary efficacy endpoint is the proportion of subjects achieving complete corneal healing as defined above.

Primary Estimand for this study will be as follow:

- Treatment regimen: CSB-001 0.1% QID, and CSB-001 vehicle QID for 8 weeks
- Target population: Subjects with stage 2 or 3 NK in at least one eye as defined by the inclusion and exclusion criteria (per Protocol Section 4), grouped per randomization assignment
- Variable of interest: Responders defined as achieving complete corneal healing as defined above.
- Intercurrent events and corresponding strategy:
  - Subjects with missing Week 8 data for any reason will be imputed as non-responders
  - Subjects who demonstrate corneal healing at Week 8 and are missing Week 10 data will be imputed as non-responders
- Population-level summary measure: Difference in the proportions of responders.

2.2.2 Secondary Efficacy Endpoints

Key secondary endpoints

- Proportion of subjects achieving corneal healing at Week 8 assessed by the CRC
- Proportion of subjects achieving corneal healing at Week 4 assessed by the CRC
- Time to corneal healing based on assessments by the CRC
- Time to ≥20% decrease in lesion size (maximum diameter) from baseline assessed by the CRC
- Proportion of subjects achieving corneal healing at each of Week 4, and Week 8 sustained for two weeks until Week 10 assessed by the investigator
- Proportion of subjects without persistent corneal staining during the study as assessed by the CRC
- Proportion of subjects with complete corneal healing and without persistent corneal staining during the study as assessed by the CRC

Other secondary endpoints

- Time to corneal healing based on assessments by the investigator
- Proportion of subjects achieving a ≥15-letter gain in the study eye from baseline in pinhole distance VA at each of Weeks 4 and 8

2.2.3 Exploratory Efficacy Endpoints

- Proportion of subjects achieving corneal healing at each of Weeks 2, 6, and 8 assessed by the CRC
- Proportion of subjects with corneal healing defined as less than 0.5 mm fluorescein staining (the lower limit of reliable slit-lamp assessment) in the lesion area, assessed by the CRC at each of Weeks 4 and 8
- Time to ≥20% decrease in lesion area from baseline assessed by the CRC
- Change in lesion size (PED or ulcer maximum diameter) from baseline at each of Weeks 2, 4, 6, 8 and 10 assessed by the CRC
- Change in lesion area (PED or ulcer) from baseline at each of Weeks 2, 4, 6, 8 and 10 assessed by the CRC
- Change in pinhole distance VA in the study eye from baseline to each of Weeks 4 and 8 (and Week 10 in the subset of subjects completing Week 10)
- Proportion of subjects achieving a ≥10-letter gain in the study eye from baseline in pinhole distance VA at each of Weeks 4 and 8
- Change in corneal sensitivity inside the lesion from baseline (measured by Cochet-Bonnet aesthesiometer) at Week 8 (data from the subset of subjects with this data)
- Change in Schirmer's test scoring at Week 8

2.2.4 Safety Endpoints

- Adverse events
- Slit-lamp examination
- Intraocular pressure (IOP)
- Dilated fundus ophthalmoscopy
- Visual acuity
- Ocular tolerability assessed by subjects

3.0 STUDY DESIGN

This is a multi-center, randomized, double-masked, vehicle-controlled, parallel-group safety and efficacy study.

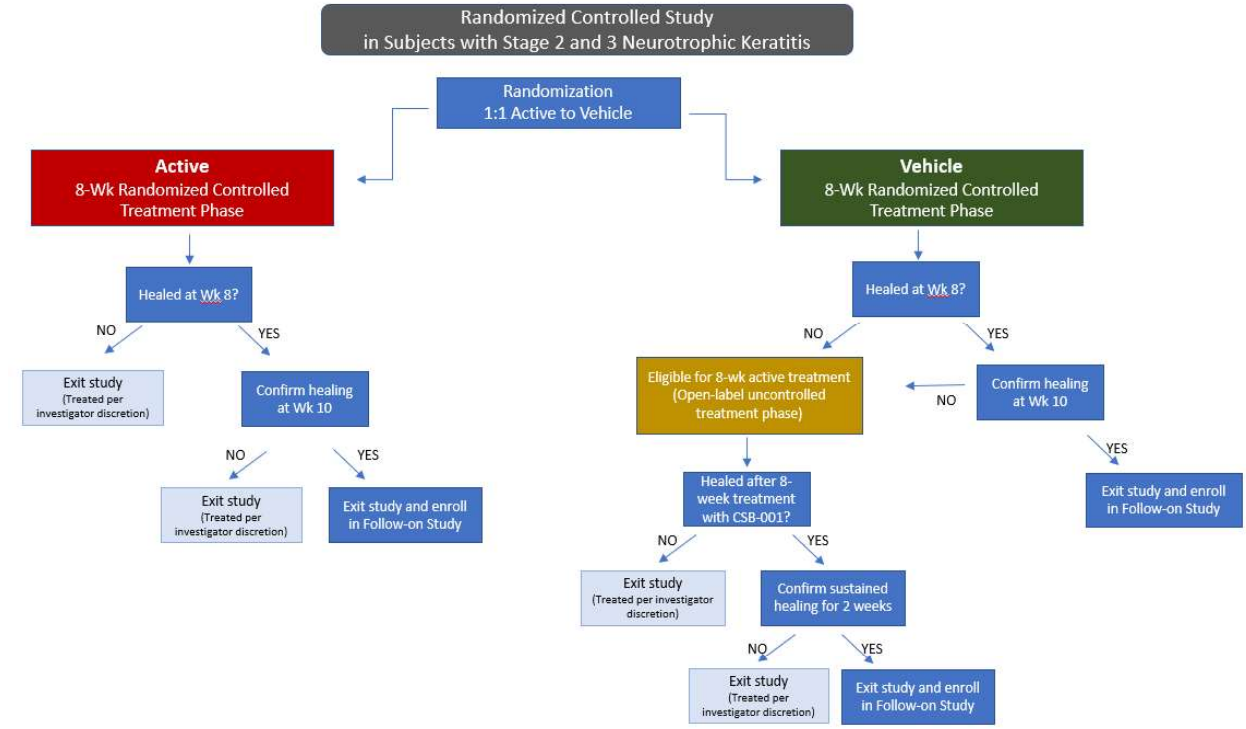
Approximately 128 subjects with stage 2 or 3 NK will be randomized in a 1:1 ratio to the CSB-001 investigational treatment arm or vehicle control arm at approximately 50 investigative sites in the United States and Canada. All subjects will provide written informed consent prior to the conduct of any study procedures at the Day 0 Screening/Randomization Visit. Subjects must meet all study inclusion and exclusion criteria to qualify for enrollment in the study. Subjects will be required to discontinue all topical ophthalmic medications and contact lens use (both therapeutic and for refractive correction) in the study eye as noted in the exclusion criteria upon enrollment. The only exceptions are the allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator and/or a non-preserved IOP-lowering topical ocular drop (with the exception of timolol) administered once-daily over the course of the study.

An initial safety phase is included whereby the first 12 randomized subjects will be evaluated by the masked Medical Monitor for dose limiting safety findings. Each subject will be assessed within three days of the Week 1 Visit. In the absence of an adverse event assessed as a dose limiting finding, enrollment of the remaining subjects will commence.

All subjects will dose with the randomized treatment QID for 8 weeks (referred to as the controlled treatment phase which includes the above initial safety phase). During the controlled treatment phase, subjects will return to the clinic weekly from Day 0 to Week 8, and again at Week 10. Subjects randomized to vehicle who are not healed at Week 8 or who are healed at Week 8 but do not remain healed at the Week 10 Visit are eligible to receive an 8-week QID course of CSB-001 (referred to as the uncontrolled treatment phase). See Schedule of Assessments, Appendix 1.

Subjects will be followed as described below based on the randomized treatment arm and Week 8 and/or Week 10 investigator assessment of corneal healing. Subjects whose cornea is not healed (deemed non-responders) at the Week 8 or Week 10 Visit will be unmasked. See Schematic of Study Design, Figure 1.

Figure 1: Schematic of Study Design



Subjects randomized to CSB-001 in the controlled treatment phase

- Subjects with corneal healing at both Weeks 8 and 10 will exit the study at Week 10.
- Subjects with corneal healing at Week 8 that is not sustained for two weeks until Week 10 will exit the study at Week 10 and be managed per investigator discretion.
- Subjects whose cornea is not healed at Week 8 will exit the study at Week 8 and be managed per investigator discretion.

Subjects randomized to vehicle in the controlled treatment phase

- Subjects with corneal healing at both Weeks 8 and 10 will exit the study at Week 10.
- Subjects with corneal healing at Week 8 that is not sustained for two weeks until Week 10 are eligible to receive an 8-week course of CSB-001 treatment (uncontrolled treatment phase).
- Subjects whose cornea is not healed at Week 8 are eligible to receive an 8-week course of CSB-001 treatment (uncontrolled treatment phase).

Subjects randomized to vehicle who are eligible for, and enter, the uncontrolled treatment phase

- Subjects with cornea healing after the 8-week course of CSB-001 (Week 8 uncontrolled treatment phase visit) that is sustained for two weeks until Week 10 will exit the study at the Week 10 uncontrolled treatment phase visit.
- Subjects with corneal healing after the 8-week course of CSB -001 (Week 8 uncontrolled treatment phase visit) that is not sustained for two weeks until Week 10

will exit the study at the Week 10 uncontrolled treatment phase visit and be managed per investigator discretion.

- Subjects whose cornea is not healed after the 8-week course of CSB-001 (Week 8 uncontrolled treatment phase visit) will exit the study and be managed per investigator discretion.

4.0 RANDOMIZATION AND BLINDING

This is a multi-center, randomized, double-masked, vehicle-controlled, parallel-group safety and efficacy study. Approximately 128 subjects (64 per treatment arm) will be randomized in the study to complete approximately 96 subjects (48 per treatment arm).

5.0 SAMPLE SIZE CONSIDERATIONS

With the assumption that the proportion of subjects that will achieve complete corneal healing for the CSB-001 and vehicle are 60% and 30%, respectively, 48 subjects per arm (a total of 96 subjects) will have 80% power to detect the difference of 30% at a two-sided alpha 0.05 based on a Chi-squared test. With a predicted dropout rate of ~10% and the risk of inadequate numbers of corneal defect images for interpretation by the central reading center at key visits (Day 0, Week 8, and Week 10), approximately 128 subjects will be randomized at 1:1 ratio (CSB-001: vehicle).

6.0 ANALYSIS POPULATIONS

6.1 Full Analysis Set (FAS)

The full analysis set will include all subjects who are randomized regardless of exposure to test article. The full analysis set will exclude subjects who did not present with stage 2 or 3 NK at the screening visit per the CRC and any subjects who have no post-baseline images. Subjects will be classified according to the treatment at randomization. The full analysis set will be the primary population for evaluating all efficacy endpoints and subject baseline characteristics.

6.2 Intention-to-Treat (ITT)

The Intention-to-Treat will include all subjects who are randomized regardless of exposure to test article. The ITT population will include subjects who did not present with stage 2 or 3 NK at the screening visit per the CRC but exclude subjects who have no post-baseline images. Subjects will be classified according to the treatment at randomization. The ITT population will be used as a supplemental analysis for evaluating the primary endpoint.

6.3 Per-protocol Set (PPS)

The per-protocol set will be a subset of FAS, excluding subjects who have any major protocol deviation which is likely to serious affect the safety and efficacy outcomes of the study. Evaluability will be assessed by subjects, visits and study procedures. The per-protocol set will be used to evaluate the primary efficacy endpoints as exploratory analyses.

6.4 Safety Analysis Set

The safety analysis set for the controlled phase will include all subjects who are randomized that receive at least one dose of test article in the controlled phase of the study. Subjects will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case subjects will be classified according to the first treatment received. The safety analysis set will be the primary population for evaluating treatment compliance and safety for the controlled phase of the study.

6.5 Safety Analysis Set – Uncontrolled phase

The safety analysis set for the uncontrolled phase will include all subjects who enter the uncontrolled phase and receive at least one dose of test article in the uncontrolled phase of the study. The safety analysis set for the uncontrolled phase will be the primary population for evaluating all uncontrolled phase data.

7.0 GENERAL STATISTICAL CONSIDERATIONS AND DEFINITIONS

7.1 General Consideration and Table Layout

The controlled phase data will be evaluated when all subjects complete the controlled phase. Data from the controlled phase will be cleaned and locked at data point level. The study will be unblinded and the controlled phase analyses will be performed. Efficacy and safety summary tables will be displayed by treatment group of CSB-001 or Vehicle.

Following completion of the last subject in the open-label, uncontrolled phase, efficacy and safety analyses based on the safety analysis set of the uncontrolled phase will be performed for the uncontrolled phase. Efficacy and safety summary tables will be displayed as a single treated group.

7.2 Baseline and Visit Windows

Baseline for the controlled phase is defined as the last non-missing assessment prior to the dosing of the study treatment. Baseline for the uncontrolled phase is defined as the last non-missing assessment prior to the dosing of the study treatment in the uncontrolled phase.

Analyses will be performed according to the scheduled visits.

7.3 Summary Statistics

- Continuous endpoints will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum and maximum values). The summary statistic n will be the number of subjects with non-missing values. All means and medians will be reported to one more significant digit than the values being analyzed. Standard deviations will be reported to two more significant digits than the values being analyzed. The minimum and maximum will be reported to the same number of significant digits as the values being analyzed.
- Categorical endpoints will be summarized as the number and percentage of participants per category. Percentages will be out of the number of subjects in the population being reported, unless otherwise noted. All percentages will be rounded to one decimal point. The number and percentage of subjects will always be presented in the form XX (XX.X) where the percentage is in parentheses. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category. Denominators for each analysis will be based on the population of interest (e.g., safety analysis set; subjects with non-missing data).
- Time to event endpoints will be summarized using Kaplan-Meier method by treatment group. Confidence intervals for the 25th, 50th and 75th percentiles will be reported, where appropriate.
- Subject listings of data will be presented for all enrolled subjects unless specified otherwise.

7.4 Data Handling Rules

There will be missing data imputation for the primary efficacy analysis. See primary efficacy analysis Section 9.1 for details.

Besides the imputations for the primary endpoint, there will be no imputation of missing data other than for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows.

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.

- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month.
- Dates with both day and month missing will be imputed as 31 Dec.
- If the ongoing flag is missing or "Yes" then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is "No" then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.
- The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

Partial/missing start dates for initial and current NK stage will be imputed as follows.

- Dates with missing day only will be imputed as the 16th of the month.
- Dates with both day and month missing will be imputed as 1 July.
- Completely missing dates will not be imputed. The current NK stage duration will be left as missing.

7.5 Study Day and Time-to-Event

For the purpose of this document and time-to-event duration calculation,

- D0 is the screening/randomization (baseline visit) day
- Time to corneal healing (0 mm lesion size) based on assessments by the CRC is defined as: the earliest Digital Imaging of Corneal Fluorescein Staining date with corneal healing, as assessed by the CRC, from the Date of randomization (D0)
- Time to corneal healing (0 mm lesion size) based on assessments by the investigator is defined as: The earliest date of investigator assessment with corneal healing from the Date of randomization (D0)
- Time to ≥20% decrease in lesion size (maximum diameter) assessed by the CRC is defined as: The earliest date of Digital Imaging of Corneal Fluorescein Staining taken with ≥20% decrease in lesion size assessed by the CRC from the Date of randomization (D0)

7.6 Interim Analyses

There is no interim analysis planned for this study.

8.0 STATISTICAL SUMMARIES

8.1 Subject Disposition

The number and percentages of subjects screened, randomized, FAS, ITT, safety analysis set, PP Set, completed the study and discontinued from the study will be reported, along with the reason for discontinuation.

Only counts will be reported for screened subjects.

8.2 Demographic and Baseline Characteristics

Demographic/baseline characteristics including age (years), sex, race, ethnicity, NK stage, and duration of current NK stage will be summarized and presented by treatment group. Descriptive statistics will be presented for the continuous variables. Frequency counts and percentages will be presented for the categorical variables for each category.

8.3 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Medical history will be summarized by system organ class (SOC) term and preferred term for each cohort by treatment group. For subjects with the same SOC and preferred term occurring more than once, the first occurrence will be tabulated. Systemic medical history and ocular medical history will be summarized separately. Ocular medical history will be summarized by study eye and non-study eye.

Conditions will be listed, including the verbatim investigator description of the relevant medical condition, the coded terms (SOC, preferred term), start date, end date, and whether or not the condition is ongoing.

8.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHO-DD), and summarized by drug class (Anatomical Therapeutic Chemical [ATC] Level 3) and preferred term; a subject will be counted only once for each medication.

Concomitant medications are medications which started 1) prior to initiation of study treatment administration and continuing for any period of time following the Day 0 administration of study treatment or 2) at any time following the Day 0 administration of study treatment. Prior medications are medications which are started before the Day 0 administration of study drug.

All medication will be listed with the prior medications flagged. Systemic prior and concomitant medication, and ocular prior and concomitant medication will be summarized separately. Ocular prior and concomitant will be summarized by study eye and non-study eye.

8.5 Protocol Deviations

Protocol deviations recorded will be reviewed and major deviations will be identified prior to database lock and unblinding of the study.

Protocol deviations will be summarized by pre-specified category from the CRF, by major or minor, and a subject listing will be presented.

8.6 Study Drug Administration

For study drug administration, descriptive statistics of the following parameters will be presented in Safety Analysis Set.

- Total number of weeks on study
- Total number of doses planned
- Total number of doses administered
- Total number of doses missed

Subject listing of study drug administration will be presented

9.0 EFFICACY EVALUATION

9.1 Primary Efficacy Endpoint

9.1.1 Primary Analyses

Analyses of the primary efficacy endpoint will follow the estimand framework stated in Section 2.2.1. Full analysis set will be used for the efficacy analyses.

The primary efficacy endpoint is the proportion of subjects achieving complete corneal healing defined as absence of corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) at Week 8 and the absence of corneal staining in the area of the defect/ulcer (i.e., 0 mm lesion) two weeks later at Week 10 as assessed by a central reading center.

Chi-squared test will be used to compare each CSB-001 active treatment group (QID) to vehicle. The proportion and associated 95% confidence interval will be reported by each treatment arm. Difference in the proportions between treatment arms and associate 95% confidence interval will also be reported.

Missing data of the primary efficacy endpoint will be imputed as follow:

- Subjects with missing Week 8 data for any reason will be imputed as non-responders
- Subjects who demonstrate corneal healing at Week 8 and are missing Week 10 data will be imputed as non-responders

9.1.2 Sensitivity Analyses

Sensitivity analyses based on different missing data imputation rules will be conducted for the primary endpoint. Specific imputation rules are:

1. Completers Analysis (Week 8 Observed) Data Imputation
   - Subjects who do not complete the Week 8 Visit will be imputed as missing
   - Subjects who demonstrate corneal healing at Week 8 and are missing Week 10 data will be imputed as missing at Week 8
2. LOCF Data Imputation
   - Subjects with missing Week 8 and/or Week 10 data will have their last observed data carried forward
3. Tipping point analyses will be performed.
   - In CSB-001 arm, one responder will be changed to be a non-responder, and the same primary analysis will be performed. In CSB-001 arm, two responders will be changed to be non-responders, and the same primary analysis will be performed again. This will continue until X responders in CSB-001 arm are changed to be non-responders when p-value becomes not statistically significant. In these analyses, no changes will be made to the vehicle arm.
   - In the vehicle arm, one non-responder will be changed to be a responder, and the same primary analysis will be performed. In the vehicle arm, two non-responders will be changed to be responders, and the same primary analysis will be performed again. This will continue until X non-responders in the vehicle arm are changed to be responders when p-value becomes not statistically significant. In these analyses, no changes will be made to the CSB-001 arm.

In addition, instead of Chi-squared test, Cochran–Mantel–Haenszel (CMH) test stratified by stage 2 NK vs stage 3 NK will be used to analyze the primary endpoint as another sensitivity analysis.

Per-protocol analysis set will also be used to analyze the primary endpoint as exploratory analyses.

9.1.3 Supplemental Analyses

Additionally, primary analysis based on ITT population will be repeated as a supplemental analysis.

9.2 Secondary Efficacy Endpoints

Key secondary endpoints

- Proportion of subjects achieving corneal healing at Week 8 assessed by the CRC
- Proportion of subjects achieving corneal healing at Week 4 assessed by the CRC
- Time to corneal healing based on assessments by the CRC
- Time to ≥20% decrease in lesion size (maximum diameter) from baseline assessed by the CRC
- Proportion of subjects achieving corneal healing at each of Week 4, and Week 8 sustained for two weeks until Week 10 assessed by the investigator
- Proportion of subjects without persistent corneal staining during the study as assessed by the CRC
- Proportion of subjects with complete corneal healing and without persistent corneal staining during the study as assessed by the CRC

The two time-to-event key secondary endpoints will be analyzed by a log-rank test at a two-sided alpha 0.05. Time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles will be reported by each treatment arm.

The two dichotomous key secondary endpoints will be analyzed using a Chi-squared test as in the analyses of the primary endpoint. The proportion and associated 95% confidence interval will be reported by each treatment arm.

Tipping point analyses will also be performed for the proportion of subjects achieving corneal healing at Week 8 assessed by the CRC.

Other secondary endpoints

- Time to corneal healing based on assessments by the investigator
- Proportion of subjects achieving a ≥15-letter gain in the study eye from baseline in pinhole distance VA at each of Weeks 4 and 8

Time to event endpoint and dichotomous endpoint will be analyzed using the same statistical method as in the analyses of the key secondary endpoints.

9.3 Exploratory Efficacy Endpoints

Descriptive summary statistics (e.g., frequency, mean, standard deviation, median, minimum, and maximum for continuous variables; frequency [%] for categorical variables) will be provided for the exploratory endpoints (see Section 2.2.3 for listing of exploratory endpoints).

10.0 SAFETY EVALUATION

10.1 Adverse Events

AEs verbatim descriptions will be coded using a current version of MedDRA. A treatment-emergent adverse event (TEAE) will be defined as any AE that occurs on or after the start time of the first study drug administration.

An overall summary of TEAEs will be presented as the number and percentage of subjects with at least one event on the following categories:

- TEAEs
- Severe TEAEs
- Treatment-related TEAEs
- Severe and treatment-related TEAEs
- Serious TEAEs
- Serious treatment-related TEAE
- TEAEs leading to treatment discontinuation
- Treatment-related TEAEs leading to treatment discontinuation
- TEAEs leading to Death (with an outcome of Fatal)

TEAEs will be summarized by System Organ Class (SOC) and Preferred Terms (PT) by treatment group. A patient will be counted only once by the highest severity grade within a system organ class and preferred term, even if the patient experienced more than 1 TEAE within a specific system organ class and preferred term. Following incidence tables of TEAEs will be presented:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- Serious TEAEs

Systemic TEAEs and ocular TEAEs will be summarized separately. Ocular TEAEs will be summarized by study eye and non-study eye.

All AEs will be listed by subjects.

SAEs for death will be listed if applicable and a narrative included.

10.2 Slit-lamp Examination

Slit-lamp examination data will be summarized by visit and by eye, and a subject listing will be presented.

10.3 Intraocular Pressure (IOP)

IOP data will be presented in a listing.

10.4 Dilated Fundus Ophthalmoscopy

Dilated fundus ophthalmoscopy data will be summarized by visit and by eye, and a subject listing will be presented.

10.5 Pinhole Distance VA

Pinhole data will be presented in a listing, besides being summarized as an exploratory endpoint.

10.6 Ocular Tolerability Questionnaire

Ocular tolerability questionnaire data will be summary by visit and a subject listing will be presented.

10.7 Urine Pregnancy

Urine pregnancy tests will be presented in a listing.

11.0 CHANGES TO THE PLANNED ANALYSES

During the analysis and reporting process, any deviations from the statistical plan designed for this protocol will be described and justified in the clinical study report.

12.0 APPENDICES

12.1 Appendix 1: Schedule of Assessments

Randomized, Double-Masked, Controlled Treatment Phase (8-week dosing; 1:1 randomization to CSB-001 or vehicle)											
Study Procedures	**Day 0[1] Screening/Randomization (Baseline Visit)**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8[2]**	**Wk 10[3]**	**Early Exit[4]**
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History (Systemic and Ocular)	X										
Previous/Change in Concomitant Meds (Systemic and Ocular)	X	X	X	X	X		X		X	X	X
Adverse Events Query	X[5]	X	X	X	X		X		X	X	X
Test Article Compliance		X	X	X	X	X	X	X	X		X
Ocular Tolerability Questionnaire[6]	X				X				X		
LogMAR Pinhole Distance VA	OU	SE[7]	SE	SE	SE		SE		OU	SE	OU
Slit-Lamp Examination	OU	SE[7]	SE	SE	SE		SE		OU	SE	OU
Digital Imaging of Corneal Fluorescein Staining	SE	SE	SE	SE	SE		SE		SE	SE	
Investigator Assessment of Corneal Healing		SE	SE	SE	SE		SE		SE	SE	
NEI Scale Assessment	SE	SE	SE	SE	SE		SE		SE	SE	
Corneal Sensitivity[8]	SE								SE		
Schirmer's Test (Non-Anesthetized)	SE								SE		
Anterior Segment OCT (at selected sites)	SE				SE				SE		

Randomized, Double-Masked, Controlled Treatment Phase (8-week dosing; 1:1 randomization to CSB-001 or vehicle)											
Study Procedures	**Day 0[1] Screening/Randomization (Baseline Visit)**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8[2]**	**Wk 10[3]**	**Early Exit[4]**
Intraocular Pressure (IOP)	**OU**								**OU**		**OU**
Dilated Fundus Ophthalmoscopy	**OU**								**OU**		**OU**
Urine Pregnancy Test (Female of Childbearing Potential)	**X**								**X**		**X**
Randomization	**X**										
Study Drug Dispensation	**X[9]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			

Note: A ±2 day visit window is allowed for all scheduled visits except for the Week 10 Visit where the window is -2 to +7 days.
OU= both eyes, SE=study eye, VA=visual acuity
[1] All procedures to be performed prior to first dose of test article except for adverse events and ocular tolerability assessments.
[2] Subjects whose cornea is healed at Week 8 will be assessed for sustained healing at Week 10. Subjects whose cornea is not healed at Week 8 will be unmasked; subjects in the CSB-001 arm will exit the study, subjects in the vehicle arm are eligible to enter the uncontrolled treatment phase and receive an 8-week course of treatment with CSB-001.
[3] Subjects whose cornea is completely healed at Week 8 and sustained until Week 10 will exit the study. Subjects whose cornea is not healed at Week 10 will be unmasked; subjects in the CSB-001 arm will exit the study, subjects in the vehicle arm are eligible to enter the uncontrolled treatment phase and receive an 8-week course of treatment with CSB-001.
[4] Ensure exit procedures are conducted at the time of study exit for subjects exiting prior to the Week 8 Visit. Only assessments not conducted as part of a planned or unscheduled study visit at the time of study exit should be performed.
[5] Record adverse events after test article instillation on Day 0
[6] Ocular tolerability assessment to be conducted immediately after in-office study drug instillation at specified visits
[7] VA and slit-lamp will be assessed in both the study and non-study eyes in the initial safety phase (i.e., first 12 subjects randomized).
[8] At Day 0, corneal sensitivity assessed using a cotton wisp will be performed to determine study eligibility. Corneal sensitivity will also be assessed using a Cochet-Bonnet aesthesiometer if available at the site. At Week 8, sensitivity will only be assessed in subjects at clinical sites with access to a Cochet-Bonnet aesthesiometer.
[9] Administer first dose in the clinic

Open-Label Uncontrolled Treatment Phase **(Subjects randomized to vehicle in the controlled treatment phase whose cornea is not healed at Week 8 or whose cornea is healed at Week 8 but not sustained for two weeks until Week 10 are eligible to receive an 8-week course of treatment with CSB-001)**												
Study Procedures	**Day 0[1*] Entering at Wk 8 Controlled Visit**	**Day 0[1*] Entering at Wk 10 Controlled Visit**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8[2]**	**Wk 10[3]**	**Early Exit[4]**
Previous/Change in Medical History and Concomitant Meds (Systemic and Ocular)			**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**
Adverse Events Query	**X[5]**	**X[5]**	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**
Test Article Compliance			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**
Ocular Tolerability Questionnaire[6]	**X**	**X**				**X**				**X**		
LogMAR Pinhole Distance VA		**NSE**	**SE**	**SE**	**SE**	**SE**		**SE**		**OU**	**SE**	**OU**
Slit-Lamp Examination		**NSE**	**SE**	**SE**	**SE**	**SE**		**SE**		**OU**	**SE**	**OU**
Digital Imaging of Corneal Fluorescein Staining			**SE**	**SE**	**SE**	**SE**		**SE**		**SE**	**SE**	
Investigator Assessment of Corneal Healing			**SE**	**SE**	**SE**	**SE**		**SE**		**SE**	**SE**	
NEI Scale Assessment			**SE**	**SE**	**SE**	**SE**		**SE**		**SE**	**SE**	
Corneal Sensitivity[7]		**SE**								**SE**		
Schirmer's Test (Non-Anesthetized)		**SE**								**SE**		
Anterior Segment OCT (at selected sites)		**SE**				**SE**				**SE**		
Intraocular Pressure (IOP)		**OU**								**OU**		**OU**
Dilated Fundus Ophthalmoscopy		**OU[8]**								**OU**		**OU**
Urine Pregnancy Test (Female of Childbearing Potential)		**X**								**X**		**X**
Study Drug Dispensation (CSB-001 0.1%)	**X[9]**	**X[9]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			

Note: A ±2 day visit window is allowed for all scheduled visits except for the Week 10 Visit where the window is -2 to +7 days.
OU= both eyes, SE=study eye, NSE=non-study eye, VA=visual acuity

*Subjects may enter the uncontrolled treatment phase at either the Week 8 or Week 10 Visit of the controlled treatment phase

- For subjects entering the uncontrolled phase at the Week 8 controlled phase visit, the assessments performed at the Week 8 controlled phase visit will serve as baseline for the uncontrolled phase in addition to the procedures noted in the table above
- For subjects entering the uncontrolled phase at the Week 10 controlled phase visit, the assessments performed at the Week 10 controlled phase visit will serve as baseline for the uncontrolled phase in addition to the procedures noted in the table above

[1] All procedures to be performed prior to the first dose of open-label treatment except for adverse events and ocular tolerability assessments
[2] Subjects whose cornea is healed at Week 8 will be assessed for sustained healing at Week 10. Subjects whose cornea is not healed at Week 8 will exit the study.
[3] Subjects whose cornea is completely healed at Week 8 and sustained until Week 10 will exit the study. Subjects whose cornea is not healed at Week 10 will exit the study.
[4] Ensure exit procedures are conducted at the time of study exit for subjects exiting prior to the Week 8 Visit. Only assessments not conducted as part of a planned or unscheduled study visit at the time of study exit should be performed.
[5] Record adverse events after instillation of open-label CSB-001 0.1% on Day 0
[6] Ocular tolerability assessment to be conducted immediately after in-office study drug instillation at specified visits
[7] Corneal sensitivity will only be assessed in subjects at clinical sites with access to a Cochet-Bonnet aesthesiometer.
[8] Per investigator discretion, an undilated fundus exam is allowed if no changes are anticipated since the exam performed at the Week 8 controlled phase visit
[9] Administer first dose in the clinic