

**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

**NCT No.:** 04909450

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8. Dispense test article according to assigned kit number using IBM CD
  - Dispense one new unopened kit; this kit is considered the back-up kit. The back-up kit dispensed at the last visit is now considered the primary kit. Instruct subject to use the remaining test articles that were dispensed at the last visit prior to opening and using the kit dispensed at this visit.
  - Remind subject regarding test article storage and administration.
  - Instruct subject that all test articles will need to be stored in the refrigerator (2-8 deg C) (or in cooler bag if away from home) until time of administration. Test article must be protected from light; instruct subject to keep vials in the pouch until the time of administration.
  - Instruct subject to keep used BFS vials and to bring to the next visit along with the subject diary
9. Schedule the subject for the next follow-up study visit (Week 3 Visit)
  - Instruct subject to bring all used and unused test articles from the opened primary kit to the visit.
  - If the back-up kit was used, instruct the subject to also bring used and unused test articles from the opened back-up kit to the visit. Unopened and unused back-up kits will be kept refrigerated at the subject's residence.

#### **6.1.4. Week 3 Visit ( $\pm 2$ day window)**

Note: Perform ophthalmic assessments in the study eye only

1. Record any changes in medical history and concomitant medications/therapies
2. Record any adverse events since the last visit
3. Assess test article compliance (including collection of used BFS vials, accountability of test articles, and review of subject diary)
4. Perform logMAR pinhole distance VA
5. Perform slit-lamp exam (without fluorescein staining)
6. Perform digital imaging of the corneal fluorescein staining
  - Two sets of images will be captured at each timepoint where digital imaging is required. The first set of images will be collected  $30 \pm 15$  seconds after fluorescein instillation. The second set of images will be collected  $120 \pm 15$  seconds after fluorescein instillation.
7. Perform investigator assessment of corneal healing and NEI scale assessment of corneal staining (additional fluorescein may be instilled per investigator discretion)
8. Dispense test article according to assigned kit number using IBM CD
  - Dispense one new unopened kit; this kit is considered the back-up kit. The back-up kit dispensed at the last visit is now considered the primary kit. Instruct subject to use

the remaining test articles that were dispensed at the last visit prior to opening and using the kit dispensed at this visit.

- Assess the inventory for the back-up kit and dispense another back-up kit as needed. In the event that additional vials are needed to complete dosing until the next follow-up visit, the back-up kit will be used.
- Remind subject regarding test article storage and administration
- Instruct subject that all test articles will need to be stored in the refrigerator (2-8 deg C) (or in cooler bag if away from home) until time of administration. Test article must be protected from light; instruct subject to keep vials in the pouch until the time of administration.
- Instruct subject to keep used BFS vials and to bring to the next visit along with the subject diary

9. Schedule the subject for the next follow-up study visit (Week 4 Visit)

- Instruct subject to bring all used and unused test articles from the opened primary kit to the visit.
- If the back-up kit was used, instruct the subject to also bring used and unused test articles from the opened back-up kit to the visit. Unopened and unused back-up kits will be kept refrigerated at the subject's residence.

**6.1.5. Week 4 Visit ( $\pm 2$  day window)**

Notes:

- Perform ophthalmic assessments in the study eye only.
  - This visit should be scheduled to coincide with one of the times for test article administration. Instruct subject to refrain from dosing until they are at the office to allow for assessment of ocular tolerability.
1. Record any changes in medical history and concomitant medications/therapies
  2. Record any adverse events since the last visit
  3. Assess test article compliance (including collection of used BFS vials, accountability of test articles, and review of subject diary)
  4. Administer the ocular tolerability questionnaire immediately after in-office administration of the test article
  5. Perform logMAR pinhole distance VA
  6. Perform slit-lamp exam (without fluorescein staining)
  7. Perform digital imaging of the corneal fluorescein staining
    - Two sets of images will be captured at each timepoint where digital imaging is required. The first set of images will be collected  $30 \pm 15$  seconds after fluorescein instillation. The second set of images will be collected  $120 \pm 15$  seconds after fluorescein instillation.

8. Perform anterior segment OCT (only at selected sites)
9. Perform investigator assessment of corneal healing and NEI scale assessment of corneal staining (additional fluorescein may be instilled per investigator discretion)
10. Dispense test article according to assigned kit number using IBM CD
  - Dispense one new unopened kit; this kit is considered the back-up kit. The back-up kit dispensed at the last visit is now considered the primary kit. Instruct subject to use the remaining test articles that were dispensed at the last visit prior to opening and using the kit dispensed at this visit.
  - Assess the inventory for the back-up kit and dispense another back-up kit as needed. In the event that additional vials are needed to complete dosing until the next follow-up visit, the back-up kit will be used.
  - Remind subject regarding test article storage and administration
  - Instruct subject that all test articles will need to be stored in the refrigerator (2-8 deg C) (or in cooler bag if away from home) until time of administration. Test article must be protected from light; instruct subject to keep vials in the pouch until the time of administration.
  - Subjects will be instructed to keep used BFS vials and to bring to the next visit along with the subject diary
11. Schedule the subject for the next follow-up study visit (Week 5 Visit)
  - Instruct subject to bring all used and unused test articles from the opened primary kit to the visit.
  - If the back-up kit was used, instruct the subject to also bring used and unused test articles from the opened back-up kit to the visit. Unopened and unused back-up kits will be kept refrigerated at the subject's residence.

**6.1.6. Week 5 Visit ( $\pm 2$  day window)**

Note: This is a drug dispensation visit; no ophthalmic assessments are required.

1. Assess test article compliance (including collection of used BFS vials, accountability of test articles, and review of subject diary)
2. Dispense test article according to assigned kit number using IBM CD
  - Dispense one new unopened kit; this kit is considered the back-up kit. The back-up kit dispensed at the last visit is now considered the primary kit. Instruct subject to use the remaining test articles that were dispensed at the last visit prior to opening and using the kit dispensed at this visit.
  - Assess the inventory for the back-up kit and dispense another back-up kit as needed. In the event that additional vials are needed to complete dosing until the next follow-up visit, the back-up kit will be used.
  - Remind subject regarding test article storage and administration

- Instruct subject that all test articles will need to be stored in the refrigerator (2-8 deg C) (or in cooler bag if away from home) until time of administration. Test article must be protected from light; instruct subject to keep vials in the pouch until the time of administration.
  - Subjects will be instructed to keep used BFS vials and to bring to the next visit along with the subject diary
3. Schedule the subject for the next follow-up study visit (Week 6 Visit)
- Instruct subject to bring all used and unused test articles from the opened primary kit to the visit.
  - If the back-up kit was used, instruct the subject to also bring used and unused test articles from the opened back-up kit to the visit. Unopened and unused back-up kits will be kept refrigerated at the subject's residence.

**6.1.7. Week 6 Visit (±2 day window)**

Refer to the Week 2 Visit (Section 6.1.3). The same procedures are performed except schedule the subject for the next follow-up study visit (Week 7 Visit).

**6.1.8. Week 7 Visit (±2 day window)**

Refer to the Week 5 Visit (Section 6.1.6). The same procedures are performed except schedule the subject for the next follow-up study visit (Week 8 Visit).

**6.1.9. Week 8 Visit (±2 day window)**

Notes:

- It is critical that all subjects return for the Week 8 Visit to ensure an adequate number of evaluable subjects for analysis. Site personnel will apply due diligence to contact the subject to return for the Week 8 Visit.
  - This visit should be scheduled to coincide with one of the times for test article administration. Instruct subject to refrain from dosing until they are at the office to allow for assessment of ocular tolerability.
  - Depending on the time of the Week 8 Visit, the subject may not be able to dose with all four doses for the day. The subject's last dose should take place in the office in order to assess ocular tolerability. Dosing will be discontinued prior to the conduct of the ophthalmic study assessments at the Week 8 Visit.
1. Collect all test articles (used and unused)
  2. Record any changes in medical history and concomitant medications/therapies
  3. Record any adverse events since the last visit
  4. Assess test article compliance (including collection of used BFS vials, accountability of test articles, and review of subject diary)

5. Administer the ocular tolerability questionnaire immediately after in-office administration of test article
6. Perform logMAR pinhole distance VA OU
7. Perform slit-lamp exam OU (without fluorescein staining)
8. Perform digital imaging of the corneal fluorescein staining in the study eye
  - Two sets of images will be captured at each timepoint where digital imaging is required. The first set of images will be collected  $30 \pm 15$  seconds after fluorescein instillation. The second set of images will be collected  $120 \pm 15$  seconds after fluorescein instillation.
9. Perform anterior segment OCT in the study eye (only at selected sites)
10. Perform investigator assessment of corneal healing and NEI scale assessment of corneal staining (additional fluorescein may be instilled per investigator discretion)
11. Assess corneal sensitivity using the Cochet-Bonnet aesthesiometer on the study eye (at select sites with a Cochet-Bonnet)
12. Perform Schirmer's test without anesthesia in the study eye
13. Perform IOP OU
14. Perform dilated ophthalmoscopy OU
15. Perform urine pregnancy test if the subject is a female of childbearing potential
16. Based on the investigator assessment of corneal healing, proceed as described below:
  - Subjects with corneal healing at Week 8 as assessed by the investigator will return at Week 10 for assessment of sustained healing. Schedule the subject for the next follow-up study visit (Week 10 Visit).
  - Subjects with incomplete corneal healing at Week 8 as assessed by the investigator will be unmasked. Sites will be provided instructions to unmask the subject using the IMB CD system.
    - Subjects randomized to vehicle will be eligible per investigator discretion to enter the uncontrolled treatment phase and receive 8-week treatment with CSB-001. See Section 6.2.
    - Subjects randomized to CSB-001 will exit the study and be treated per investigator discretion. See Section 6.3 for the study procedures required to be completed at the time of study exit.

**6.1.10. Week 10 Visit (-2 to + 7 day window)**

Notes:

- It is critical that all subjects assessed as healed by the investigator at Week 8 return for the Week 10 Visit to ensure an adequate number of evaluable subjects for analysis. Site personnel will apply due diligence to contact the subject to return for the Week 10 Visit, even if outside the visit window. Subjects who return for the

Week 10 Visit more than 7 days than the actual visit date may not be eligible to enter the uncontrolled treatment phase.

- In cases where the CRC and investigator healing assessment differs at Week 8 and/or 10 (i.e., CRC assessed as healed and investigator assessed as not healed), and the subject did not enter the uncontrolled treatment phase, the Sponsor may request the subject to return to the clinic. At that visit, digital imaging of the cornea and logMAR pinhole distance VA will be completed at a minimum. The visit may be out of window and is acceptable.
  - Perform ophthalmic assessments in the study eye only
1. Record any changes in medical history and concomitant medications/therapies
  2. Record any adverse events since the last visit
  3. Perform logMAR pinhole distance VA
  4. Perform slit-lamp exam (without fluorescein staining)
  5. Perform digital imaging of the corneal fluorescein staining
    - Two sets of images will be captured at each timepoint where digital imaging is required. The first set of images will be collected  $30 \pm 15$  seconds after fluorescein instillation. The second set of images will be collected  $120 \pm 15$  seconds after fluorescein instillation.
  6. Perform investigator assessment of corneal healing and NEI scale assessment of corneal staining (additional fluorescein may be instilled per investigator discretion)
    - Subjects with corneal healing at Week 10 as assessed by the investigator will exit this study.
    - Subjects with incomplete corneal healing at Week 10 as assessed by the investigator will be unmasked. Sites will be provided instructions to unmask the subject using the IBM CD system.
      - Subjects randomized to vehicle will be eligible per investigator discretion to enter the uncontrolled treatment phase and receive 8-week treatment with CSB-001. See Section 6.2.
      - Subjects randomized to CSB-001 will exit the study and be treated per investigator discretion.

## **6.2. Open-Label Uncontrolled Treatment Phase**

Subjects randomized to the vehicle arm in the controlled treatment phase with either incomplete corneal healing at the Week 8 controlled phase visit or corneal healing at the Week 8 controlled phase visit that is not sustained for two weeks (until Week 10) will be eligible to enter the uncontrolled treatment phase and receive CSB-001 treatment.

The uncontrolled treatment phase includes the same number of visits as that for the controlled treatment phase. The procedures required for the uncontrolled treatment phase is identical to that

of the controlled treatment phase (see Section 6.1) except for the baseline visit which is described below.

Note: A  $\pm 2$  day visit window is allowed for all scheduled visits except for the Week 10 uncontrolled phase visit where the window is -2 to +7 days.

#### **6.2.1. Day 0 Uncontrolled Phase Visit (Baseline for Uncontrolled Phase)**

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

##### **6.2.1.1. Subject entering the uncontrolled phase at the Week 8 controlled phase visit**

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 listed below:

1. Dispense open-label test article according to assigned kit numbers using the IBM CD system
  - Each subject will be dispensed sufficient test article for 2 weeks of dosing (i.e., 2 kits). Each kit will contain 7 pouches, one for each day of dosing. Each pouch will contain 4 single-use BFS vials, sufficient for one day of dosing. One kit is sufficient for 7 days of QID dosing. One kit will be considered the primary kit and will be opened while at the clinic and used for dosing. The second kit will be considered the back-up kit.
  - Instruct subject to use all test articles from the primary kit prior to opening and using the back-up kit
  - Instruct subject to store test articles in the refrigerator (2-8 deg C) (or in cooler bag if away from home) until the time of administration. Test article must be protected from light; instruct subject to keep vials in the pouch until the time of administration.
  - The first dose of test article should be administered while at the office by the subject under observation of the study staff. Open one pouch from the primary kit and remove one BFS single-dose vial and instill one drop in the study eye.
  - Instruct the subject on proper test article instillation including handling of test article BFS vials. In the event that a full drop is not instilled, instruct subject to instill another drop.
  - Instruct subject to administer test article four-times per day (approximately 4 hours apart) for 8 weeks. Note: Depending on the time of the Day 0 Visit, the subject may not be able to dose all four doses on the initial day. The subject will be instructed by the site staff to dose at the suggested remaining dosing times (i.e., subjects examined around noon will administer 3 total doses on Day 0, subjects examined late afternoon will administer 2 total doses on Day 0.
  - Instruct subject on how to complete the subject diary
  - Instruct subject to keep used BFS vials and to bring to the next visit along with the subject diary

2. Administer the ocular tolerability questionnaire immediately after in-office administration of test article
3. Record any adverse events after test article instillation
4. Schedule the subject for the next follow-up study visit (Week 1 Visit)
  - Instruct subject to bring all used and unused test articles from the opened primary kit to the visit.
  - If the back-up kit was used, instruct the subject to also bring used and unused test articles from the opened back-up kit to the visit.
  - Unopened and unused back-up kits will be kept refrigerated at the subject's residence.

**6.2.1.2. Subjects entering the uncontrolled phase at the Week 10 controlled phase visit**

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 listed below.

1. Perform logMAR pinhole distance VA in the non-study eye
2. Perform slit-lamp exam in the non-study eye (without fluorescein staining)
3. Perform anterior segment OCT in the study eye (only at selected sites)
4. Assess corneal sensitivity using the Cochet-Bonnet aesthesiometer in the study eye (at select sites with a Cochet-Bonnet)
5. Perform Schirmer's test without anesthesia in the study eye
6. Perform IOP OU
7. Perform dilated fundus ophthalmoscopy OU (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)
8. Perform urine pregnancy test if the subject is a female of childbearing potential
9. Perform procedures 1-4 noted in Section 6.2.1.1 above.

**6.2.2. Week 1 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 1 Visit of the controlled treatment phase (see Section 6.1.2).

**6.2.3. Week 2 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 2 Visit of the controlled treatment phase (see Section 6.1.3).

**6.2.4. Week 3 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 3 Visit of the controlled treatment phase (see Section 6.1.4).

**6.2.5. Week 4 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 4 Visit of the controlled treatment phase (see Section 6.1.5).

**6.2.6. Week 5 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 5 Visit of the controlled treatment phase (see Section 6.1.6).

**6.2.7. Week 6 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 6 Visit of the controlled treatment phase (see Section 6.1.7).

**6.2.8. Week 7 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 7 Visit of the controlled treatment phase (see Section 6.1.8).

**6.2.9. Week 8 Uncontrolled Phase Visit ( $\pm 2$  day window)**

Perform procedures as described above for the Week 8 Visit of the controlled treatment phase (see Section 6.1.9).

- Subjects with corneal healing at the Week 8 uncontrolled phase visit as assessed by the investigator will return for the Week 10 uncontrolled phase visit for assessment of sustained healing. Schedule the subject for the next follow-up study visit (Week 10 uncontrolled phase visit).
- Subjects with incomplete corneal healing at the Week 8 uncontrolled phase visit as assessed by the investigator will exit the study and be treated per investigator discretion.

**6.2.10. Week 10 Uncontrolled Phase Visit (-2 to +7 day window)**

Perform procedures as described above for the Week 10 Visit of the controlled treatment phase (see Section 6.1.10).

- Subjects with corneal healing at the Week 10 uncontrolled phase visit as assessed by the investigator will exit this study.
- Subjects with incomplete corneal healing at the Week 10 uncontrolled phase visit as assessed by the investigator will exit the study and be treated per investigator discretion.

**6.3. Early Exit/Study Discontinuation**

Listed below are the procedures required for subjects exiting the study prematurely prior to the Week 8 Visit (in both controlled and uncontrolled treatment phases). Only assessments not completed or conducted as part of a planned or unscheduled study visit on the same day that the subject exits the study are required to be performed. Site personnel should make all efforts to bring the subject back to the site to complete the exit procedures.

1. Collect all test articles (used and unused)
2. Record any changes in concomitant medications/therapies
3. Record any adverse events since the last visit
4. Assess test article compliance (including collection of used BFS vials, accountability of test articles, and review of subject diary)
5. Perform logMAR pinhole distance VA OU (if study eye has been assessed at the same visit, only perform in the non-study eye)
6. Perform slit-lamp exam OU (if study eye has been assessed at the same visit, only perform in the non-study eye)
7. Perform IOP OU (if study eye has been assessed at the same visit, only perform in the non-study eye)
8. Perform dilated ophthalmoscopy OU (if study eye has been assessed at the same visit, only perform in the non-study eye)
9. Perform urine pregnancy test (on female subjects of childbearing potential)
10. Exit subject from the study

#### **6.4.        Unscheduled Visit**

Unscheduled visits can be used for assessment of an adverse event or at the discretion of the investigator prior to a subject's next scheduled study visit. Procedures and examinations conducted at the Unscheduled Visit are at the discretion of the investigator.

### **7.           STUDY PROCEDURES AND ASSESSMENTS**

Refer to the Schedule of Assessments ([Table 2](#)) for the required procedures and assessments to be performed over the course of the study. Refer to the Schematic of Study Design ([Figure 2](#)) for an overview of the study. Evaluations by study visit are described in Section 6. A separate Manual of Procedures will provide further details on some of the procedures listed below.

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject.

#### **7.1.        Informed Consent Procedure**

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent.

The Sponsor will provide to investigators a proposed informed consent form that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the exclusion criteria Section 4.2.

## **7.2. Subject Screening**

Subjects will be screened and if eligible for the study will be randomized on the same day (Day 0 Visit of the controlled treatment phase). Any subject not meeting study enrollment requirements will be considered a screen failure and will not be randomized into the study. Reason for screen failure will be documented. Subjects may rescreen at a future date if their eligibility changes.

## **7.3. Subject Demographics**

Subject demographics (birth date, ethnicity, sex, race) will be collected on all subjects at the Day 0 Visit of the controlled treatment phase.

## **7.4. Concomitant Medications**

All medications/therapies received within the past 3 months prior to the Day 0 Visit of the controlled treatment phase will be collected. Changes in concomitant medications will be assessed at each study visit. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured. Medications will be coded using the most recent version of the World Health Organization Drug Dictionary (WHO-DD).

## **7.5. Medical History**

Relevant medical history and current conditions (systemic and ocular) will be collected at the Day 0 Visit of the controlled treatment phase prior to the administration of the first dose of test article. Changes in medical history will be assessed at visits after the first dose. Subject medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

## **7.6. Ocular Tolerability**

Ocular tolerability will be assessed using a self-reported subject questionnaire administered by the site staff. This assessment will be completed immediately after the in-office test article administration at specified visits.

## **7.7. Pinhole Distance Visual Acuity**

LogMAR pinhole distance visual acuity will be assessed monocularly at all applicable visits using the ETDRS visual acuity chart starting from a distance of 4 meters (13 feet). This

assessment is to be performed prior to any examination requiring contact with the eye and pupil dilation. Refer to the Manual of Procedures for additional information.

### **7.8. Intraocular Pressure**

Intraocular pressure (IOP) should be performed using Goldmann tonometry. At the discretion of the investigator, a tonopen may be used. IOP assessment must be performed after assessments of corneal healing and after other assessments which may be impacted by application of anesthesia for IOP. The measurement method used for a subject should remain consistent throughout the study.

### **7.9. Slit-Lamp Biomicroscopy**

Slit lamp exam of the eyelids, conjunctiva, cornea, anterior chamber, iris, and lens will be performed.

### **7.10. Dilated Fundus Ophthalmoscopy**

A dilated fundus examination of the retina, macula, choroid, optic nerve (including C/D ratio) and vitreous will be performed. VA and IOP must be performed prior to pupil dilation for the fundus ophthalmoscopy exam. As dilating drops will be instilled, this procedure must be performed after assessments of corneal healing.

For subjects entering the uncontrolled phase at the Week 10 controlled phase visit, an undilated fundus exam is allowed in the event that the investigator does not anticipate any change since the exam performed at the Week 8 controlled phase visit.

### **7.11. Schirmer's Test without Topical Anesthesia**

Tear production will be evaluated by Schirmer's test without anesthesia. A sterile tear flow strip is inserted into the lower temporal lid margin of each eye. The room is dimly lit, and the subject asked to close their eyes. After 5 minutes, the strip is removed, and the length of the moistened area is measured.

### **7.12. Corneal Sensitivity Assessment**

Corneal sensitivity will be assessed by the investigator at the Day 0 Visit of the controlled treatment phase as part of the screening procedures to determine study eligibility. This assessment may be performed with a cotton wisp per standard of care clinical practice. At sites with a Cochet-Bonnet aesthesiometer, corneal sensitivity will also be assessed and recorded with the Cochet-Bonnet device.

Subjects eligible for the study must meet the following inclusion criteria: clinical evidence of decreased corneal sensitivity within the area of the PED or corneal ulcer and outside of the area of the defect in at least one corneal quadrant in the study eye in the opinion of the investigator assessed using a cotton wisp.

For sites with access to a Cochet-Bonnet aesthesiometer, corneal sensitivity will also be assessed at study visits specified in the Schedule of Events. Corneal sensitivity will be assessed in the area of the PED or corneal ulcer. In the event that the NK defect has healed, the investigator should

test in the area of the original lesion. This assessment is measured in centimeters to the nearest half centimeter.

### **7.13. Digital Imaging of Corneal Fluorescein Staining**

Digital imaging of corneal fluorescein staining will be performed prior to any procedures that touches the eye and prior to instillation of any topical agents except for fluorescein.

This procedure will be performed using a slit-lamp equipped with a camera after instillation of fluorescein (using a fluorescein strip and non-preserved saline) into the lower palpebral conjunctiva. Two sets of images will be captured at each timepoint where digital imaging is required per the Schedule of Events. **The first set of images will be collected  $30 \pm 15$  seconds after fluorescein instillation. The second set of images will be collected  $120 \pm 15$  seconds after fluorescein instillation.** Capturing the photos at the specified times is critical to ensure appropriate staining of the NK lesion. Additional images may be captured to ensure quality images are obtained.

Images will be uploaded electronically to a portal for assessment by masked readers at the study designated central reading center (CRC). Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. Refer to the reading center manual for additional information.

In the event that fluorescein was instilled for another procedure on the same day prior to digital imaging, wait at least 2 hours before re-instilling fluorescein, then perform imaging.

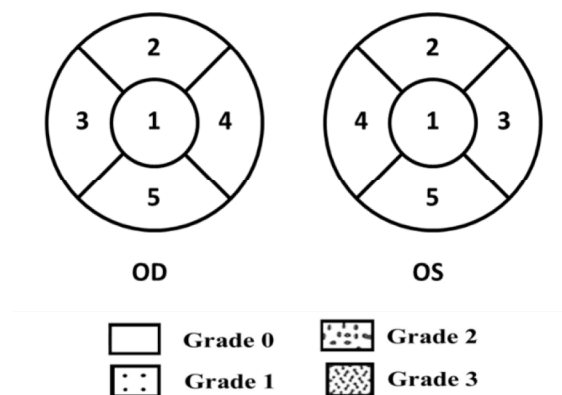
### **7.14. Investigator Assessment of Corneal Healing**

Assessment of corneal healing will be conducted by the investigators via direct slit-lamp examination of corneas stained with fluorescein. A binary assessment will be performed by the investigator: healed or not healed based on slit-lamp observation of the presence of re-epithelialization of the corneal defect (i.e., PED or ulcer). In an eye assessed by the investigator as not healed via slit-lamp exam, the investigator will immediately view the digital images taken of the fluorescein staining at the same visit to validate his/her assessment of re-epithelialization status and the final investigator determination will be recorded.

Depending on the time lapse from the digital imaging procedure to the investigator assessment of corneal healing, additional fluorescein may be instilled per investigator discretion.

### **7.15. NEI Scale Assessment of Corneal Staining**

Corneal fluorescein staining will be assessed using the cornea NEI scale. The scale relies on a chart that divides the cornea into five sections. A standardized grading system of 0 (absent) to 3 (severe) is used for each of the five areas on the cornea. Grade 0 is specified when no staining is present, and the maximum score is 15. This scale will be used by investigators and the CRC.



## 7.16. Anterior Segment Optical Coherence Tomography (AS-OCT)

AS-OCT may be performed at select investigative sites as an exploratory assessment. AS-OCT will be performed after digital imaging of corneal fluorescein imaging but prior to any procedures that touches the eye and prior to instillation of any topical agents except for fluorescein.

Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. Refer to the reading center manual for additional information.

## 7.17. Urine Pregnancy Test

A urine pregnancy test will be performed on female subjects who are of childbearing potential in the both the controlled and uncontrolled treatment phases (at the Day 0 Visit and at the completion of the 8-week controlled treatment period).

# 8. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL

## 8.1. Early Discontinuation of Study Treatment

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

The following is a list of possible reasons for study treatment discontinuation and/or subject withdrawal from the study:

- Subject withdrawal of consent

- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol deviation that results in a significant risk to the subject's safety requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Patient self-reports pregnancy during the study period prior to or at the Week 8 Visit (or at the end of the uncontrolled treatment period if applicable)
- Investigator decision (e.g., progressive disease)
- Dose limiting finding as determined by the medical monitor and the Sponsor in subjects who are part of the initial safety phase

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.

All participants who discontinue study treatment should come in for a follow-up visit as soon as possible and then should be encouraged to complete all remaining regularly scheduled visits and follow-up procedures.

In the event that a subject prematurely discontinues the study, site personnel should make all efforts to bring the subject back to the site to complete the Exit Procedures. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

## **9. EARLY STUDY TERMINATION**

The study can be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs of the early termination of the trial.

## **10. PROTOCOL DEVIATIONS**

A protocol deviation occurs when the subject, investigator, or the Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria. Investigators ascertain they will apply due diligence to avoid protocol deviations. Significant protocol deviations for this study include, but are not limited to, the following:

- Randomization in absence of meeting inclusion/exclusion criteria
- Use of prohibited medications/treatments

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Sponsor will determine if a protocol deviation results in withdrawal of a subject.

When a protocol deviation occurs, it will be discussed with the investigator and a Protocol Deviation Form detailing the deviation will be generated. This form will be signed by a Sponsor representative and the investigator. A copy of the form will be filed in the site's regulatory binder and in the files of the Sponsor.

## **11. STUDY MEASURES**

### **11.1. Assessment of Efficacy**

Efficacy endpoints are described below with more details provided in Section 17 Statistical Methods and Considerations and the Statistical Analysis Plan for the study.

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.

#### **11.1.1. Primary Efficacy Endpoint**

The primary efficacy endpoint is the proportion of subjects achieving complete corneal healing as defined above in Section 11.1.

#### **11.1.2. 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  $\geq 20\%$  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  $\geq 15$ -letter gain in the study eye from baseline in pinhole distance VA at each of Weeks 4 and 8

**11.1.3. 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  $\geq 20\%$  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  $\geq 10$ -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

**11.2. Assessment of Safety**

**11.2.1. Safety Parameters**

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

## 12. ADVERSE AND SERIOUS ADVERSE EVENTS

### 12.1. Adverse Event (AE) Definition and Reporting

An adverse event (AE) is any untoward medical occurrence associated with the use of a study drug in humans, whether or not it is considered related to the study drug. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug. Lack of efficacy of the study treatment for the condition being investigated is not an AE.

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. AEs will be recorded from the signing of consent form until the end of the study.

The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Severity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated with no disruption of normal activities)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2. An AE of severe intensity may not be considered serious.

An investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

The relationship of an AE to the test article should be assessed according to the following guidelines:

Definitely	Previously known toxicity of investigational product or known complication of procedure; or an event that follows a reasonable temporal sequence from administration of the investigational product or procedure; that follows a known or expected response pattern to the suspected investigational product or procedure; if suspected investigational product is confirmed by stopping or reducing the dosage of the investigational product; and that is not explained by any other reasonable hypothesis.
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Probably	An event that follows a reasonable temporal sequence from administration of the investigational product or procedure; that follows a known or expected response pattern to the investigational product or procedure; if suspected investigational product is confirmed by stopping or reducing the dosage of the investigational product; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the investigational product or procedure; that follows a known or expected response pattern to that investigational product or procedure; but that could readily have been produced by a number of other factors.
Unlikely	The temporal sequence of the event with the study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.
Unrelated	An event that can be determined with certainty to have no relationship to the investigational product or procedure.

The investigator must record all AEs and SAEs in the source documents and report the data on the appropriate CRF pages. The investigator will notify the local EC per the EC requirements.

The information recorded will be based on the signs or symptoms reported by the subject. A clinical diagnosis should be provided to the extent feasible instead of listing individual signs or symptoms and should be recorded clearly in a concise manner using standard, acceptable medical terminology to eliminate vague, ambiguous, or colloquial expressions.

The Sponsor is responsible for ongoing collection of safety data and their evaluation in accordance with local and federal guidelines and regulatory requirements. The Sponsor will inform all central ECs, investigators (if applicable), and regulatory authorities of findings that could adversely affect the safety of subjects or impact the conduct of the study and will report to regulatory authorities in conformity with expedited and periodic reporting requirements.

If a subject withdraws due to one or more AEs, the investigator should record only a single event (i.e., the primary AE) as the reason for withdrawal on the CRF whenever possible.

## 12.2. Serious Adverse Event (SAE) Definition and Reporting

A serious adverse event is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- A congenital abnormality or birth defect

- Is an important medical event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Note that an AE or suspected adverse reaction is considered “life-threatening” for reporting as an SAE if, in the view of either the investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Study sites will document all SAEs that occur (whether or not related to study treatment). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed. All SAEs should be followed to resolution or until the Investigator deems the event to be chronic or the subject to be stable. The Sponsor may contact the investigator to obtain additional information on any SAE that has not resolved at the time the subject completes the study.

In accordance with the standard operating procedures and policies of the local IRB, the site investigator will report SAEs to the IRB.

All SAEs must be reported by the investigative site personnel to the Sponsor within 24 hours of the first awareness of the event. The investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to the Sponsor. Additional follow-up information, if required or available, should be provided to the Sponsor within one working day of receipt and kept in the site study file. Serious AE reporting instructions will be provided by the Sponsor.

### **12.3. Suspected Pregnancy (Exposure-in-Utero)**

Female subjects of childbearing potential will be instructed to contact the investigator immediately if they suspect they might be pregnant. If pregnancy is confirmed, study drug must be discontinued, and the subject must be withdrawn from the study. The subject should be followed until completion of the pregnancy.

Should a pregnancy occur, it must be reported and recorded on a designated pregnancy report form. The investigator should inform the Sponsor immediately of the pregnancy and provide any available follow-up information, including perinatal and neonatal outcome, on a pregnancy report form. Other appropriate follow-up procedures should be considered if indicated. Infants resulting from such pregnancies should be followed for 6 weeks to assess for developmental milestones. The sponsor may contact the Investigator to request additional information throughout the course of the pregnancy.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

## **13. STATISTICAL METHODS AND CONSIDERATIONS**

### **13.1. Sample Size Determination**

With the assumption that the proportion of subjects that will achieve complete corneal healing (defined in Section 11.1) 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. Considering 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).

### **13.2. Analysis Populations**

#### **13.2.1. Full Analysis Set**

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. 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.

#### **13.2.2. Safety Analysis Set**

The safety analysis set for the controlled phase will include all subjects who are randomized and have received at least one dose of test article. 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.

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.

### **13.3. Efficacy Analysis**

The full analysis set will be the primary population for evaluating all efficacy endpoints. All efficacy analyses are based on study eye. If both eyes are affected with NK, the eye with the higher stage assessed by the investigator using a slit-lamp will be deemed the study eye. If both eyes are of the same stage, the eye with the larger defect per investigator assessment will be the study eye. If the above is equal between the eyes, the right eye will be deemed the study eye. Only the study eye will be treated.

#### **13.3.1. Analysis of Primary Endpoint**

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 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. The primary efficacy endpoint

will be analyzed using a Chi-squared test at a two-sided alpha 0.05. The proportion and associated 95% confidence interval will be reported by each treatment arm.

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

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

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.

### 13.3.2. Analysis of Secondary 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  $\geq 20\%$  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 five dichotomous key secondary endpoints will be analyzed using a Chi-squared test at a two-sided alpha 0.05. The proportion and associated 95% confidence interval will be reported by each treatment arm.

#### **Other secondary endpoints**

- Time to corneal healing based on assessments by the investigator
- Proportion of subjects achieving a  $\geq 15$ -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.

#### **13.3.3. Analysis of Exploratory 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 11.1.3 for listing of exploratory endpoints).

#### **13.4. Safety Analysis**

The safety analysis set will be the primary population for safety evaluation. Summaries of AEs and other safety parameters will be provided by treatment arm, as appropriate.

AEs verbatim descriptions will be coded using a current version of the Medical Dictionary for Regulatory Activities (MedDRA).

An overall summary of subjects with AEs and SAEs will be tabulated with numbers and percentages of subjects and repeated for severity and relationship to study drug per treatment group. A subject will be counted only once by the highest severity grade within a system organ class and preferred term, even if the subject experienced more than one AE within a specific system organ class and preferred term. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized.

The incidence of AEs and SAEs will be summarized by body system and treatment group. All AEs and SAEs will be listed by subjects.

Descriptive summary statistics (e.g., n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) for other safety parameters will be summarized by visit. Changes from baseline of safety parameters will also be summarized.

#### **13.5. Interim Analysis**

No interim analysis is planned for this study.

## **14. DATA COLLECTION, RETENTION AND MONITORING**

### **14.1. Data Collection Instruments**

The investigator is responsible for all information collected on participants enrolled in this study and must maintain detailed records on all enrolled subjects. The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with study drug.

An electronic data capture (EDC) system will be used for the study. Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. The electronic data capture system (Title 21 CFR Part 11 compliant) will be managed by a data management vendor. Password-protected access to the database will be granted to authorized study personnel based on their role after training on the use of the system. Accuracy of the data will be verified by source data verification at regular intervals, and all corrections to data will be made in the database. Participants will be identified by a site number and participant number and will not be identified by name in the study database or on any study documents to be collected by the Sponsor.

All data collected over the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the eCRF will remain at the Investigator's site at the completion of the study.

### **14.2. Data Management Procedures**

The data will be entered into a validated database. The data management vendor will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

### **14.3. Data Quality Control and Reporting**

The data clarification process will be managed within the electronic data capture system by either system-generated or manually-generated queries. After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be electronically documented through the system audit trail.

### **14.4. Archival Data**

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the EDC host company in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of final reports), data for analysis is locked and cleaned per established procedures.

#### **14.5. Availability and Retention of Investigational Records**

The investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor, IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each participant must be maintained that includes the signed Participant Informed Consent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records.

All records relating to the conduct of this study are to be retained by the investigator until notified in writing by the Sponsor when it is acceptable to dispose of any study records. To comply with international regulations, documentation relating to the study should be retained by the investigator for at least two years after the last marketing application approval, or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the investigator may need to retain these documents for a longer period if required by the local regulatory requirements or by an agreement with the Sponsor.

#### **14.6. Monitoring**

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor, and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

The Sponsor will monitor this clinical study through site monitoring visits and remote data checks to assess the adequacy of study site personnel and facilities and to ensure adherence to the protocol, study procedures, and applicable regulations. The monitor will also assess proper eCRF completion and source document retention.

The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sponsor and/or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the investigator.

During the study, a monitor from the Sponsor will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are accurately recorded in the case report forms, and that investigational product accountability checks are performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

## **15. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS**

### **15.1. Ethical Conduct of the Study**

The study is to be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) and according to the Declaration of Helsinki and applicable regulatory requirements (including Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312)).

### **15.2. Subject Confidentiality**

The processing of subjects' personal data for this study will be limited to those data that are reasonably necessary to investigate the utility of the study drug used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws. The Sponsor, whose responsibilities require access to personal data, agrees to keep the identity of study subjects confidential. This confidentiality must be maintained throughout the complete data processing. To maintain confidentiality, all evaluation forms, reports and other records will be identified by a coded number and initials only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

### **15.3. Protocol Amendments**

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate

safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the IRBs are notified within five working days.

#### **15.4. Institutional Review Board (IRB)**

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the investigator will keep the IRB informed as to the progress of the study. The investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, written information provided to subjects or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated (i.e., before enrollment of any subject into the study). The IRB's unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

#### **15.5. Informed Consent Form (ICF)**

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a, b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and provide the documents to the Sponsor for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will

send an IRB-approved copy of the Informed Consent Form (ICF) to the Sponsor for the study file.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

If appropriate and required by the local IRB, assent from the participant will also be obtained. If a participant is unable to sign the ICF, a legal representative may sign for the participant. A copy of the signed consent form (and assent) will be given to the participant or legal representative of the participant and the original will be maintained with the participant's records.

## **15.6. Publications**

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **15.7. Investigator Responsibilities**

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when to protect the safety, rights or welfare of participants.
4. Personally conduct or supervise the study (or investigation).
5. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
6. Report to the Sponsor any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor.
9. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to participants or others (to include amendments and IND safety reports).
11. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/participants.

12. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

### **15.8. Data Safety Monitoring Board**

A Data Safety Monitoring Board will not be used for this study. The safety of subjects will be monitored by investigators and by the Medical Monitor on an ongoing basis.

### **15.9. Participant Confidentiality**

In order to maintain participant confidentiality, only a site number and participant number will identify all study participants on eCRFs, and other documentation submitted to the Sponsor. Additional participant confidentiality issues (if applicable) are covered in the Clinical Trial Agreement.

### **15.10. Audits and Inspections**

Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

## 16. LIST OF REFERENCES

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## 17. APPENDICES

**Table 2: Schedule of Assessments**

Randomized, Double-Masked, Controlled Treatment Phase (8-week dosing; 1:1 randomization to CSB-001 or vehicle)												
Study Procedures	Screening/Randomization (Baseline Visit)	Day 0 <sup>1</sup>	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8 <sup>2</sup>	Wk 10 <sup>3</sup>	Early Exit <sup>4</sup>
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 <sup>5</sup>	X	X	X	X		X		X	X	X
Test Article Compliance			X	X	X	X		X		X		X
Ocular Tolerability Questionnaire <sup>6</sup>		X				X				X		
LogMAR Pinhole Distance VA		OU	SE <sup>7</sup>	SE	SE	SE		SE		OU	SE	OU
Slit-Lamp Examination		OU	SE <sup>7</sup>	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 <sup>8</sup>		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								OU		OU
Urine Pregnancy Test (Female of Childbearing Potential)		X								X		X
Randomization		X										
Study Drug Dispensation		X <sup>9</sup>	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

All procedures to be performed prior to first dose of test article except for adverse events and ocular tolerability assessments.

## Protocol CSB-C20-003

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<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> Record adverse events after test article instillation on Day 0

<sup>6</sup> Ocular tolerability assessment to be conducted immediately after in-office study drug instillation at specified visits

<sup>7</sup> V/A 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).

<sup>8</sup> 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.

<sup>9</sup> 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 <sup>1*</sup> Entering at Wk 8 Controlled Visit	Day 0 <sup>1*</sup> Entering at Wk 10 Controlled Visit	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8 <sup>2</sup>	Wk 10 <sup>3</sup>	Early Exit <sup>4</sup>
Previous/Change in Medical History and Concomitant Meds (Systemic and Ocular)			X	X	X	X		X		X	X	X
Adverse Events Query	X <sup>5</sup>	X <sup>5</sup>	X	X	X	X		X		X	X	X
Test Article Compliance			X	X	X	X	X	X	X	X		X
Ocular Tolerability Questionnaire <sup>6</sup>	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 <sup>7</sup>		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 <sup>8</sup>								OU		OU
Urine Pregnancy Test (Female of Childbearing Potential)		X								X		X
Study Drug Dispensation (CSB-001 0.1%)	X <sup>9</sup>	X <sup>9</sup>	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

<sup>1</sup> All procedures to be performed prior to the first dose of open-label treatment except for adverse events and ocular tolerability assessments

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> Record adverse events after instillation of open-label CSB-001 0.1% on Day 0

<sup>6</sup> Ocular tolerability assessment to be conducted immediately after in-office study drug instillation at specified visits

<sup>7</sup> Corneal sensitivity will only be assessed in subjects at clinical sites with access to a Cochet-Bonnet aesthesiometer.

<sup>8</sup> 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

<sup>9</sup> Administer first dose in the clinic

Figure 2: Schematic of Study Design

