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

Document Date: 21 July 2023

CSB-001 Ophthalmic Solution 0.1%

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 APPROVAL PAGE

The protocol has been approved by Claris Biotherapeutics, Inc.

Sponsor's Authorized Officer:

July 25, 2023

Susan C. Orr, OD
Chief Medical Officer
Claris Biotherapeutics

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CSB-001 ophthalmic solution 0.1%. I have read the Protocol CSB-C20-003 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Version 1.0	27April2021
Version 2.0 (Amendment 1)	18June2021
Version 3.0 (Amendment 2)	31May2022
Version 4.0 (Amendment 3)	12July2023
Version 5.0 (Amendment 4)	21July2023

Overall Rationale for Amendment 1 (Version 2.0):

Section #	Description of Change	Brief Rationale
Throughout protocol	Minor editorial changes throughout document	To provide clarifications
Throughout the protocol	Minor revision in the definition of complete corneal healing for the primary efficacy endpoint	To provide clarifications
Section 4.1	Revised inclusion 3: From: Subjects with stage 2 (PED) or stage 3 (corneal ulcer) NK. Subjects with bilateral NK may enroll in the study but only one eye will be selected as the study eye (worse eye) and be treated with test article. The study eye may not be treated with Oxervate concurrently. To: Subjects with stage 2 (PED) or stage 3 (corneal ulcer) NK. Subjects with bilateral NK may enroll in the study but only one eye will be selected as the study eye (worse eye) and be treated with test article.	Treatment will be left to investigator discretion including the use of Oxervate in the non-study eye concurrently.
Section 4.1	Revised inclusion 5: From: Subjects with 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 with a cotton wisp, or the Cochet-Bonnet aesthesiometer if available at the site). To: Subjects with 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 assessed using a cotton wisp.	The cotton wisp test for corneal sensitivity assessment is a standard of care clinical practice for diagnosis of NK.

Section #	Description of Change	Brief Rationale
Section 4.2	Revised exclusion 4: From: Monocular subject (subjects with one functioning eye defined as having any ocular pathology that results in a pinhole distance visual acuity 20/100 or worse [Snellen]). To: Subjects with fellow eye (non-study eye) pinhole distance visual acuity 20/100 or worse (Snellen).	To provide clarifications
Section 4.2	Deleted exclusion 6: Subjects with severe vision loss in the study eye with no potential for visual improvement in the opinion of the investigator as a result of the study treatment.	Decision to enroll subject per investigator discretion
Synopsis, Sections 4.3, 6	Eliminated requirement for preservative-free antibiotic eye drops.	The use of antibiotic eyes drops will be at the discretion of the investigator
Section 6	Ordering of ophthalmic procedures revised to ensure that digital imaging of the corneal fluorescein staining	
Sections 6, 7	Revision made to require pinhole distance visual acuity vs best-corrected distance visual acuity	In this subject population, refractions made be variable and may not be accurate
Sections 6, 7	Clarified digital imaging of corneal fluorescein staining requirement to require two sets of images to be captured at each timepoint where digital imaging is required. The first set of images will be collected 30 ± 15 seconds after fluorescein instillation. The second set of images will be collected 120 ± 15 seconds after fluorescein instillation.	Images taken at two different timepoints provides additional data,
Sections 6, 7	Use of Cochet-Bonnet device to assess corneal sensitivity to be done by sites with access to the device. Sites without the device will not perform this assessment.	Leverage sites with Cochet-Bonnet device to generate quantitative data for corneal sensitivity and accommodate sites without the device.
Sections 6.1.2, 6.1.4	Require digital imaging at Weeks 1 and 3 in all eyes, regardless of healing status per investigator assessment.	Collecting images at Weeks 1 and 3 will provide additional data for healing at early timepoints.

Section #	Description of Change	Brief Rationale
Section 7	Eliminate requirement for confocal microscopy for the study	Limited sites with confocal microscopy capability. Plan for separate study to assess confocal microscopy.
Section 7	Clarifications made to study procedures and assessments. A separate Manual of Procedures will provide additional details on some of the procedures and assessments.	Editorial and to provide clarifications
Table 2	Schedule of events updated to reflect current study procedures and order of conduct.	Editorial

Overall Rationale for Amendment 2 (Version 3.0)

Section #	Description of Change	Brief Rationale
Synopsis and where applicable in the protocol	• Revision to the number of study centers participating in the trial from up to 26 to approximately 40 • Addition of Canada to US as countries with sites participating in the trial	Given the low prevalence of stage 2 and 3 NK, increasing the number of sites and including sites in Canada will aid in the enrollment of the study
Synopsis, Section 4.1	• Inclusion 4: From: Subjects with no clinical evidence of improvement in the PED or corneal ulcer within the 2 weeks prior to study enrollment despite the use of conventional non-surgical treatments for neurotrophic keratitis (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses [either silicone hydrogel or rigid gas permeable]) as determined by the investigator or referring physician's medical record. To: Subjects with no clinical evidence of improvement in the PED or corneal ulcer within the 2 weeks prior to study enrollment despite the use of conventional non-surgical treatments for neurotrophic keratitis	Provides clarification on the inclusion criteria.

Section #	Description of Change	Brief Rationale
	(e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses [either silicone hydrogel or rigid gas permeable]) as determined by the investigator or referring physician's medical record. a. No clinical evidence of improvement is defined as no improvement and/or fluctuation in the aspects of the PED/ulcer that in the opinion of the investigator does not demonstrate progression towards resolution over the previous 2 weeks. • Inclusion 6: From: Pinhole distance visual acuity score ≤ 75 ETDRS letters measured with a LogMAR chart (≥ 0.2 LogMAR, ≤ 20/32 Snellen or ≤ 0.625 decimal fraction) in the study eye. To: Pinhole distance visual acuity score ≤ 75 ETDRS letters measured with a LogMAR chart (≥ 0.2 LogMAR, 20/32 or worse Snellen or ≤ 0.625 decimal fraction) in the study eye.	
Synopsis, Section 4.2	• Deleted exclusion 4 of version 2.0: Subjects with fellow eye (non-study eye) pinhole distance visual acuity 20/100 or worse (Snellen). • Due to the deletion, subsequent exclusion criteria were renumbered.	Revision made to expand the NK patient population eligible for the study. These revisions are not expected to negatively impact subject safety.
Synopsis, Section 4.2	Revisions to the following exclusion criteria (note the exclusion criteria number reflects version 3.0): • Exclusion 2: From:	Revisions made to expand the NK patient population eligible for the study. These revisions are not expected to negatively impact subject safety.

Section #	Description of Change	Brief Rationale
	'Previous use of Oxervate in the study eye within the past 4 months.' To: 'Previous use of Oxervate in the study eye with last administration within the past 2 months.' • Exclusion 3: From: 'Any other ocular disease that will require topical ocular treatment in the study eye over the course of the study.' To: 'Any other ocular disease, except glaucoma, that will require topical ocular treatment in the study eye over the course of the study.' • Exclusion 4: From: 'Use of any other topical treatments other than the study medication provided by the Sponsor and allowed by the study protocol can be administered to the study eye over the course of the study. The only exception is the allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator.' To: 'Use of any other topical treatments other than the study medication provided by the Sponsor and allowed by the study	

Section #	Description of Change	Brief Rationale
	protocol can be administered to the study eye over the course of the study. The following are exceptions: a) Allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator b) Allowance for use of a non-preserved IOP-lowering prostaglandin topical ocular drop administered once-daily (QD) in glaucomatous eyes over the course of the study.' • Exclusion 8: From: 'Prior surgical procedure(s) for the treatment of NK (e.g., tarsorrhaphy, conjunctival flap, etc.) within the past 6 months.' To: 'Prior surgical procedure(s) for the treatment of NK (e.g., partial or complete tarsorrhaphy, conjunctival flap, etc.) within the past 2 months.'	
Section 4.3	Revised to allow use of a non-preserved IOP-lowering prostaglandin topical ocular drop dosed once-daily in glaucomatous eyes over the course of the study.	Change made to be consistent with change in exclusion criteria.
Section 7.2	Added language to allow for rescreening at a future date if the patient's eligibility changes.	Given the low incidence of stage 2 and 3 NK, allowance of rescreening if the patient's eligibility changes will aid in the enrollment of the study and provide opportunities for patients to be included in the trial.
Section 7.13	Added the statement: Additional images may be captured to ensure quality images are obtained.	Clarification to allow for additional images to be taken by the site as needed
Section 7.15	Added image of cornea NEI scale.	Included as recommended by FDA.

Section #	Description of Change	Brief Rationale
Sections 14 and 15	References to HREC (Human Research Ethics Committee) deleted	References to IRB is sufficient.
Throughout protocol	References to follow-on observational study deleted.	The conduct of the follow-on study is independent of the current study.

Overall Rationale for Amendment 3 (Version 4.0)

Section #	Description of Change	Brief Rationale
Synopsis and throughout protocol	Sample size changed from 108 to 128 randomized subjects. Minor changes to sample size justification.	Increased sample size to reduce 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) supportive of the primary endpoint for each study arm.
Synopsis	Study period revised from Jan 2023 to June 2024	Extended timeline to enroll additional subjects
Synopsis, Sections 3.1, 4.2, 4.3	Revised exclusion #4 to allow for use of any non-preserved IOP-lowering topical ocular drop, with the exception of timolol, administered once-daily (QD) in glaucomatous eyes over the course of the study	Revision made to expand the NK patient population eligible for the study. This revision is not expected to negatively impact subject safety.
Synopsis and throughout protocol	Clarified that PI assessment of corneal healing at Weeks 8 and/or 10 will determine eligibility to continue in the uncontrolled treatment phase. It is not feasible for the CRC to provide real-time assessment of healing given time required to review images and provide feedback.	For clarification
Synopsis, Sections 11 and 13	Key secondary endpoints revised	Additional secondary endpoints added and re-ordered

Section #	Description of Change	Brief Rationale
Synopsis, Sections 11 and 13	Clarifications made to exploratory efficacy endpoints	For clarification
Synopsis and Section 13	Definitions for full analysis set and safety analysis set revised as detailed below: 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. The full analysis set will be the primary population for evaluating all efficacy endpoints and subject baseline characteristics. 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. 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.	Revised to accommodate
Section 6.1.10	Added to procedures: In cases where the CRC and investigator assessment of healing 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.	To allow for additional images to be captured in subjects whose healing status differs between the investigator and CRC assessment.

Section #	Description of Change	Brief Rationale
Section 7.15	Minor editorial changes made to cornea NEI scale. The scale will be used by both the investigator and CRC.	For clarification
Overall Rationale for Amendment 2 (Version 3.0) table	The correct inclusion referenced should be inclusion 6 and not inclusion 5. The table has been corrected.	For clarification

Overall Rationale for Amendment 4 (Version 5.0)

Section #	Description of Change	Brief Rationale
Synopsis and Sections 3.1, 4.2, 4.3	Revision to exclusion 3 to allow subjects with elevated intraocular pressure which includes ocular hypertension and glaucoma. Deleted the term *glaucomatous eyes* from exclusion 4 to consider eyes with elevated intraocular pressure which includes ocular hypertension and glaucoma. Revised criteria below: 3. Any other ocular disease, except elevated intraocular pressure (i.e., ocular hypertension or glaucoma), that will require topical ocular treatment in the study eye over the course of the study. 4. Use of any other topical treatments other than the study medications provided by the Sponsor and allowed by the study protocol can be administered to the study eye over the course of the study. The following are exceptions: a) Allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator. b) Allowance for use of a non-preserved IOP-lowering topical ocular drop administered once-daily (QD) over the course of the study. Timolol is prohibited.	Clarification to allow for eyes with elevated intraocular pressure which includes ocular hypertension and glaucoma to be considered for the study.
List of Abbreviations and Definitions of Terms	Added CRC for Central Reading Center	Editorial

Section #	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes Table: Document History	Corrected date for Version 4.0, Amendment 3 from 10July2023 to 12July2023	Editorial

SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company:
Claris Biotherapeutics, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product:
CSB-001 ophthalmic solution 0.1%</td></tr>
<tr><td colspan="3">Name of Active Ingredient:
Oremepermin-α (Human recombinant dHGF [5-amino acid deleted hepatocyte growth factor])</td></tr>
<tr><td>Protocol Number:
CSB-C20-003</td><td>Phase: 1/2</td><td>Country: US</td></tr>
<tr><td colspan="3">Title of Study:
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</td></tr>
<tr><td colspan="3">Study center(s): Multi-center (Approximately 50 investigational sites in the US and Canada)</td></tr>
<tr><td colspan="2">Studied period (years):
Estimated date first subject enrolled: June2021
Estimated date last subject completed: June2024</td><td>Phase of development:
Phase 1/2</td></tr>
<tr><td colspan="3">Objective:
The 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.</td></tr>
<tr><td colspan="3">Study Design:
Multi-center, randomized, double-masked, vehicle-controlled, parallel-group safety and efficacy study.

Study Overview:
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 for therapeutic and refractive correction) in the study eye as noted in the exclusion criteria upon enrollment. The following are exceptions:
a) Allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator.
b) Allowance for use of a non-preserved IOP-lowering topical ocular drop administered once-daily (QD) over the course of the study. Timolol is prohibited.</td></tr>
</table>

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 following approximately seven days of dosing in the study eye. 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. See Schedule of Assessments, Table 2.

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. See Schematic of Study Design, Figure 2.

- Subjects in either treatment group deemed healed at both Weeks 8 and 10 will exit the study.
- Subjects whose cornea is not healed (deemed non-responders) at the Week 8 or Week 10 Visit will be unmasked.
    - Subjects randomized to CSB-001 who are not healed at Week 8, or who are healed at Week 8 but not sustained for two weeks until Week 10 will exit the study and be managed per investigator discretion.
    - Subjects randomized to vehicle who are not healed at Week 8, or who are healed at Week 8 but not sustained for two weeks until Week 10 are eligible to receive an 8-week QID course of CSB-001 (referred to as the uncontrolled treatment phase).

Number of Subjects (planned):

Approximately 128 subjects will be randomized in the study to complete approximately 96 subjects (48 in each treatment arm).

Sample Size Justification:

Assuming the proportion of subjects that will achieve complete corneal healing is 60% for the CSB-001 group and 30% for the vehicle group, 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. Complete corneal healing is defined in the Statistical Methods section below. 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).

Inclusion Criteria:

1. Subjects must be willing to read, understand, and give informed consent and sign and date the Informed Consent form before any study-related procedures is performed. The Informed Consent form signed by subjects must have been approved by the IRB for the current study.
2. Male or female subjects 18 years of age or older.
3. Subjects with stage 2 (PED) or stage 3 (corneal ulcer) NK. Subjects with bilateral NK may enroll in the study but only one eye will be selected as the study eye (worse eye) and be treated with test article.

4. Subjects with no clinical evidence of improvement in the PED or corneal ulcer within the 2 weeks prior to study enrollment despite the use of conventional non-surgical treatments for neurotrophic keratitis (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses [either silicone hydrogel or rigid gas permeable]) as determined by the investigator or referring physician's medical record.
    a. No clinical evidence of improvement is defined as no improvement and/or fluctuation in the aspects of the PED/ulcer that in the opinion of the investigator does not demonstrate progression towards resolution over the previous 2 weeks.
5. Subjects with 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 assessed with a cotton wisp.
6. Pinhole distance visual acuity score ≤ 75 ETDRS letters measured with a LogMAR chart (≥ 0.2 LogMAR, 20/32 or worse Snellen or ≤ 0.625 decimal fraction) in the study eye.
7. Subjects must have the ability and willingness to comply with study procedures.

Exclusion Criteria:

Unless noted, the criteria below refer to the study eye.

1. Any active ocular infection (bacterial, viral, fungal, or protozoal) or active ocular inflammation not related to NK in either eye in the opinion of the investigator. Infectious epithelial keratitis including herpetic keratitis (i.e., dendritic lesions or geographic ulcers) in either eye is excluded. Subjects on oral antibiotic at the time of screening are eligible but should continue the medication for the duration of the study.
2. Previous use of Oxervate in the study eye with last administration within the past 2 months.
3. Any other ocular disease, except elevated intraocular pressure (i.e., ocular hypertension or glaucoma), that will require topical ocular treatment in the study eye over the course of the study.
4. Use of any other topical treatments other than the study medications provided by the Sponsor and allowed by the study protocol can be administered to the study eye over the course of the study. The following are exceptions:

    a) Allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator.

    b) Allowance for use of a non-preserved IOP-lowering topical ocular drop administered once-daily (QD) over the course of the study. Timolol is prohibited.
5. Schirmer's test without anesthesia ≤3 mm/5 minutes.
6. History of any ocular surgery (including laser procedures) within the 6 months before study enrollment with the exception of cataract surgery which is excluded within 3 months prior to screening. An exception to the preceding statements is allowed if the ocular surgery was considered the cause of the stage 2 or 3 NK.
7. Anticipated need for or planned ocular surgery over the course of the study.
8. Prior surgical procedure(s) for the treatment of NK (e.g., partial or complete tarsorrhaphy, conjunctival flap, etc.) within the past 2 months.

9. Anticipated need for amniotic membrane over the course of the study. Prior treatment with amniotic membrane (sutured or sutureless) within 6 weeks of enrollment or within 2 weeks after the membrane has disappeared or has been removed within the area of the PED or ulcer.
10. Prior treatment with autologous serum within 2 weeks of enrollment.
11. Subjects treated with Botox (botulinum toxin) injections to induce pharmacologic blepharoptosis within 90 days prior to enrollment in the study and the pharmacologic blepharoptosis has not resolved in the opinion of the investigator.
12. Anticipated need to use therapeutic contact lenses or contact lens wear for refractive correction over the course of the study. Use of any contact lens is not permitted during the study.
13. Anticipated need for punctal occlusion or punctal plugs over the course of the study. Subjects with non-dissolvable punctal plugs inserted prior to the study are eligible for enrollment provided that the plug is maintained during the study and promptly replaced if lost during the study. Short-term dissolvable plugs are allowed if inserted >2 weeks of screening. Long-term dissolvable plugs are allowed if inserted >4 months of screening.
14. Evidence of corneal ulceration involving the posterior third of the corneal stroma, corneal melting or perforation in the opinion of the investigator.
15. Presence or history of any ocular or systemic disorder or condition that might hinder the efficacy of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or could be judged by the investigator to be incompatible with the study visit schedule or conduct (e.g., progressive or degenerative corneal or retinal conditions other than NK or associated sequelae, uveitis, optic neuritis, poorly controlled diabetes, autoimmune disease, immunocompromised, systemic infection, neoplastic diseases). Keratoconus is excluded with the exception of subjects with a history of keratoconus who are post-transplant as the surgery may be the underlying cause of NK.
16. Any need for, or anticipated change in, the dose of systemic medications known to impair the function of the trigeminal nerve (e.g., antidepressants, neuroleptics, antipsychotics, and antihistamines) during the study period. These treatments are allowed during the study provided that they are initiated more than 30 days before study enrollment and are expected to remain stable throughout the course of the study treatment periods. Note that PRN use of these medications as a sleep aid is allowed.
17. Known hypersensitivity to any components of the test articles provided as part of the study, or procedural medications (e.g., fluorescein).
18. History of drug, medication, or alcohol abuse or addiction within the past 3 years.
19. Use of any investigational agent within 30 days of the Screening/Randomization Visit.
20. Participation in another clinical study at the same time as the present study.
21. Females of childbearing potential (those who are not surgically sterilized or postmenopausal for at least 1 year) will be excluded from participation in the study if they meet any one of the following conditions:
    a. are pregnant or,

b. have a positive result on the urine pregnancy test at screening or,
c. intend to become pregnant during the study treatment period or,
d. are breast-feeding or,
e. not willing to use highly effective birth control measures, such as: hormonal contraceptives –oral, implanted, transdermal, or injected and/or mechanical barrier methods –spermicide in conjunction with a barrier such as a condom or diaphragm or intrauterine device (IUD) during the entire course of and 30 days after the study treatment periods.

Investigational Product, Dosage and Mode of Administration:

- CSB-001 ophthalmic solution 0.1%
- Topical ocular administration
- Eye drop instilled topically onto the surface of the eye four times daily approximately 4 hours apart (QID) in the study eye for 8 weeks

Reference Product, Dosage and Mode of Administration:

- CSB-001 vehicle solution
- Topical ocular administration
- Eye drop instilled topically onto the surface of the eye four times daily approximately 4 hours apart (QID) in the study eye for 8 weeks

Duration of treatment:

Up to 8 weeks (56 days) treatment duration

Criteria for Evaluation:

Safety

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

Efficacy

Corneal healing definitions

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 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).

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

Primary efficacy endpoint

Proportion of subjects achieving complete corneal healing as defined above.

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

Statistical Methods:

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. The full analysis set will be the primary population for evaluating all efficacy endpoints and subject baseline characteristics.

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. 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.

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.

See Section 13 of the protocol for details on the statistical methods and considerations.

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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 (HGF receptor)
CRC	Central Reading Center
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)
rhHGF	recombinant human hepatocyte growth factor
SAE	serious adverse event
SAP	Statistical Analysis Plan

1. INTRODUCTION

1.1. Background on Neurotrophic Keratitis

Neurotrophic keratitis (NK), also known as neurotrophic keratopathy or neurotrophic keratoconjunctivitis, is a rare and sight-threatening degenerative corneal disease with an estimated prevalence of 1.6-4.2 cases per 10,000 persons (National Organization for Rare Disorders, Sacchetti 2014, Pflugfelder 2020, Mastropasqua 2017). NK affects approximately 6% of herpetic keratitis cases, 12.8% of herpes zoster keratitis cases and 2.8% of patients who underwent surgical procedures for trigeminal neuralgia (Sacchetti 2014). The pathognomonic sign of NK is reduced, or absent, corneal sensitivity caused by impairment of the ophthalmic branch of the trigeminal nerve (cranial nerve V), from the trigeminal nucleus to the corneal nerve endings, resulting in compromised corneal epithelial and ocular surface integrity.

NK is classified as an orphan disease. Due to the low prevalence of NK, there is sparse epidemiological data published. Prior to the recent approval of cenegermin (recombinant nerve growth factor ophthalmic solution), no pharmacological therapy was indicated for the treatment of NK. The most comprehensive sources of available NK patient demographic information include FDA and EMA reviews of the cenegermin BLA and MAA, respectively. The study subject's NK history, captured at enrollment, provides evidence supporting the chronic nature of NK. In the two cenegermin pivotal studies, subjects were diagnosed with NK (any stage) an average of 2.3±4.6 years and 2.7±7.6 years prior to enrollment in the EU and US studies, respectively. The average times from initial stage 2 or 3 NK diagnosis at enrollment were reported as 1.4±3.5 years (EU) and 0.6±1.0 years (US). In the absence of eliminating or controlling the underlying cause(s) of the disease (e.g., lid abnormalities, diabetes, herpetic keratitis), it may be considered that NK is a longer standing, chronic disease rather than an acute, single episode condition and thus warrants long-term physician care and/or repeat therapy (Trinh 2020). Maintaining corneal integrity reduces the risk for vision loss associated with persistent epithelial defects, ulcers, and progression to stromal melting and corneal perforation (Pflugfelder 2020, Saad 2020, Bonini 2018, European Medicines Agency, Food and Drug Administration).

The cornea, lacrimal glands, conjunctiva, and eyelids are innervated by sensory branches of the ophthalmic division of the trigeminal nerve (Dua 2018). The corneal nerves and corneal epithelial cells are mutually supportive and crosstalk between the two regulates the integrity, proliferation, differentiation, migration, and adhesion of the ocular surface cells. Corneal nerves release neuromodulators that provide trophic support to the epithelium stimulating wound healing and maintaining anatomic integrity. In turn, corneal epithelial cells and keratocytes release neuropeptides, neurotrophins, and growth factors that influence survival, differentiation, and maturation of nerve fibers (Mastropasqua 2017, Tervo 1997, Schmid 2005, Nakamura 2010). A reduction in sensory-mediated reflexes (such as tearing and blinking) and diminished production of trophic factors by corneal nerves renders the ocular surface more susceptible to injury (Sacchetti 2014, Mastropasqua 2017, Dua 2018, You 2000). Damage to the trigeminal nerve leads to impairment of corneal protective reflexes and degeneration of corneal nerves with a corresponding decrease in trophic supply leading to corneal epithelial breakdown, loss of epithelial cell neural support, and decreased ability of the cornea to recover from damage which can lead to corneal ulceration, melting, and perforation (Sacchetti 2014, Mastropasqua 2017, Dua 2018).

Ocular and systemic conditions associated with nerve damage at any level to the fifth cranial nerve, from the trigeminal nucleus to the corneal nerve endings, may lead to the development of NK. The etiologies of NK are diverse and include infections, systemic comorbidities, central nervous system insults, corneal dystrophies, toxic injuries, and genetic and iatrogenic causes. The most common causes of nerve damage include herpetic keratitis (herpes simplex or varicella zoster), corneal surgery, chemical burns, long-term use of contact lenses, ablative procedures for trigeminal neuralgia, and surgical procedures for reduction of jaw fractures. Other less frequent causes are space-occupying intracranial masses (e.g., schwannoma, meningioma, and aneurysms) that can lead to compression of the nerve and reduce nerve function and corneal sensitivity. Systemic diseases that may compromise trigeminal function like diabetes, multiple sclerosis and Leprosy may lead to the development of NK (Dua 2018, Versura 2018, Mantelli 2015, Hsu 2015). In approximately one-third of NK eyes, the disease is multi-factorial increasing the complexity of identifying the underlying cause (Saad 2020).

The diagnosis, prognosis, and treatment of NK are based on presenting symptoms, disease severity, and etiology. NK is grouped into three stages according to the Mackie classification (Mackie 1995). This staging is based on increasing severity of corneal compromise from least to greatest. Stage 1 (mild) NK exhibits ocular surface irregularities and potentially reduced vision; stage 2 (moderate) NK exhibits a persistent or recurrent epithelial defect with reduced vision, and stage 3 (severe) NK exhibits corneal ulceration involving stromal tissue and significantly reduced vision. Corneal sensitivity, underpinned by nerve damage, is increasingly reduced to absent in NK eyes as severity and duration increases.

Treatment of NK aims to accelerate epithelial healing and restore corneal integrity, reducing the risk for permanent vision loss resulting from infection and/or fibrosis. Treatments for NK can be classified as topical, systemic, protective, or surgical and often a combination of approaches is considered. Conventional therapies for stage 1 aim to prevent further epithelial breakdown and include non-standardized treatments, such as preservative-free artificial tears, discontinuation of toxic topical medications, autologous serum eye drops and therapeutic contact lenses. Therapies for stage 2 and 3 aim to accelerate epithelial regeneration, and prevent corneal thinning and ulceration reducing the risk for scarring and permanent vision loss. Treatments include surgeries and procedures to restore ocular surface integrity (e.g., tarsorrhaphy, botulinum-induced ptosis, conjunctival flap, amniotic membrane transplantation, corneal transplantation). While it is well documented in the literature that palliative treatments for NK can promote corneal epithelial regrowth over a neurotrophic lesion, most stage 1 treatments provide short-term efficacy for a chronic condition. And while surgical interventions can be effective, they are often performed late, carry the risk of infection and/or corneal scarring and resultant poor vision, and/or are cosmetically undesirable to patients (Di Zazzo 2019). Cenegermin, the first drug indicated for the treatment of NK, is approved by both US FDA (2018) and EU EMA (2017). FDA's approval is without limit to stage, while the EU approval is limited to moderate and severe NK (European Medicines Agency, Food and Drug Administration). In pivotal trials, stage 2 and 3 NK subjects administered cenegermin ophthalmic solution, 20 ug/mL (Oxervate®) demonstrated significantly faster healing of the corneal epithelium than patients treated with the vehicle solution (Bonini 2018, Pflugfelder 2020). However, the rate of NK recurrence was numerically but not statistically greater in the NK groups than the control groups across both studies (12.2% and 9.7% more in the NK groups compared to vehicle at Week 24 post-treatment in the EU and US study, respectively) (Pflugfelder 2020, Food and Drug Administration).

NK is a vision threatening, potentially chronic, orphan eye disease where an unmet need exists for novel efficacious and safe treatments. The goal of treatment is to restore and maintain corneal integrity as NK can progress to ulcer, stromal melting and corneal perforation with associated risk for profound vision loss resulting from irreversible corneal scarring. Claris Biotherapeutics, Inc. (Claris) is developing CSB-001 (dHGF ophthalmic solution 0.1%) for the treatment of neurotrophic keratitis.

1.2. Background on dHGF

Hepatocyte growth factor (HGF) is an endogenous, physiologically active substance that was identified, purified, and cloned as a factor to stimulate the growth of mature hepatocytes (Nakamura 1984, Russell 1984, Nakamura 1987, Gohda 1988, Zarnegar 1989, Nakamura 1989, Miyazawa 1989, Tashiro 1990, Seki 1990). It was demonstrated that HGF has various biological activities, such as growth stimulation, migration promotion, differentiation induction, anti-apoptosis, and organogenesis and angiogenesis inducing actions, on not only hepatocytes but also many kinds of cells as targets (Montesano 1991, Matsumoto 2014, Birchmeier 1998, Funakoshi 2003, Nakamura 2011, Honda 1995, Hamanoue 1996, Maina 1999, Maina 1997, Ohya 2007). Through these activities, HGF is involved in tissue construction and organogenesis during the developmental process and in tissue reconstruction during tissue repair and regeneration.

Preclinical studies designed to address the therapeutic significance of HGF have been performed on injury/disease models, including acute tissue injury, chronic fibrosis, cardiovascular, and neurodegenerative diseases. The promotion of cell growth, survival, migration, and morphogenesis that is associated with extracellular matrix proteolysis are the biological activities that underlie the therapeutic actions of HGF. Recombinant HGF and the expression vectors for HGF are biological drug candidates for the treatment of patients with diseases and injuries that are associated with impaired tissue structure and/or function.

dHGF is a glycoprotein consisting of 692 amino acids with an α-chain of 458 amino acids and a β-chain of 234 amino acids bound together by a disulfide bond. CSB-001 drug substance is a sterile, purified preparation of human rh dHGF (the splice variant of HGF with a 5 amino acid deletion in the first kringle domain) produced recombinantly in mammalian cell culture (Chinese hamster ovary (CHO) cells).

Both dHGF and HGF are endogenous, naturally occurring proteins differing by only 5 amino acids in the kringle 1 region. The two isoforms do not have differing efficacy profiles across multiple in vivo efficacy models including those conducted by Claris. Shima et al reported that the deletion significantly altered the solubility and immunological properties of HGF (Shima 1994). HGF was respectively about 20-, 10-, and 2-fold more potent than dHGF in the stimulation of DNA synthesis in human umbilical vein endothelial cells, human aorta smooth muscle cells, and NSF-60 (murine myeloblastic cells). Conversely, dHGF was respectively about 3-, 2-, and 2-fold more potent than HGF in the stimulation of DNA synthesis in LLC-PK1 (pig kidney epithelial cells), OK (American opossum kidney epithelial cells), and rat hepatocytes. HGF was over 70-fold more soluble than dHGF in PBS. The structural change in HGF may be responsible for its altered biological activities and solubility and dHGF was selected as a drug candidate for the cornea over HGF based on these differences.

Activation of the HGF-c-Met pathway results in biological responses that support morphogenesis, regeneration, the survival of cells and tissues, nerve regeneration, and reduced fibrosis. Characterizations of conditional c-MET knockout mice demonstrate that the HGF-Met pathway plays an important role in regeneration, protection, and homeostasis in various cells and tissues, which includes hepatocytes, renal tubular cells, and neurons. The potential therapeutic benefits of dHGF are well-suited to NK pathophysiology.

HGF accelerates corneal epithelial healing and reduces and reverses corneal scarring by sequential regulation of molecular and cellular events to lessen fibrosis. HGF modulates inflammation and promotes corneal epithelial cell proliferation and ordered epithelial regeneration (Omoto 2017) and inhibits TGF-β induced conversion of fibroblasts into scar-inducing myofibroblasts (Mittal 2016). Further, HGF induces apoptosis in preformed myofibroblasts (Gupta 2018) and enhances production of matrix metalloproteinase (MMP) enzymes (e.g., MMP1 and MMP10). These MMPs have been implicated in reducing accumulation of disorganized extracellular matrix (ECM) proteins including fibronectin and collagens that contribute to fibrosis (Rohani 2015, Iimuro 2008, McMahan 2016).

Table 1 shows the molecular pathways of dHGF and the functional activity that supports a potential therapeutic benefit for patients with neurotrophic keratitis.

Table 1: Molecular Pathways of dHGF and the Functional Benefit

Function	**Molecular Pathway**	**HGF**
Cell Survival/Anti-Apoptotic	AKT	+
Cell Proliferation	MAPK/ERK	+
Neurite outgrowth	PLCγ	+
Axonal elongation	FAK	+
Cell Migration	FAK	+
Anti-fibrotic	SMAD7/SMURF1	+
Anti-inflammatory	BtK/IL1Ra/PDL1/IL10	+

Completed non-clinical animal model studies were conducted by Massachusetts Eye and Ear Institute (MEEI) with mouse HGF (mHGF) and recombinant human HGF and repeated by Claris at a contract laboratory with rh dHGF drug substance (0.1% and 0.2%) and mHGF compared to controls. The results across labs were consistent and support the potential efficacy of CSB-001 ophthalmic solution 0.1% in accelerating healing in NK thereby reducing the window of time for onset of infection and fibrosis. dHGF and HGF were evaluated in mechanical wound and bacterial injury (LPS) in vivo murine models by Claris and MEEI academic institution and in an ex vivo mechanical would healing porcine model by MEEI.

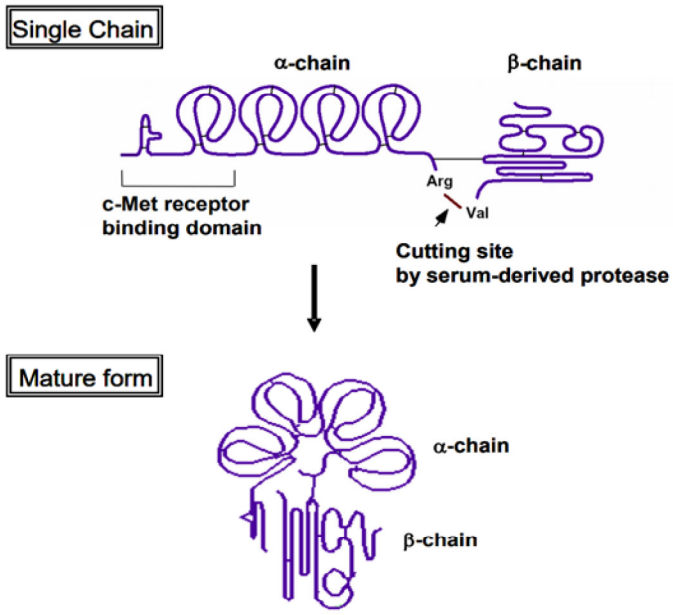
The systemic tolerability, safety, and pharmacokinetics of dHGF have been well-characterized in GLP studies following single and repeat systemic (IV, intrathecal [IT]) and local (topical skin, vocal cord fold injection) administration in multiple species (including rodents, rabbits, dogs, and nonhuman primates). A full battery of safety pharmacology studies was conducted with dHGF administered by intravenous injection. There were no test article-related effects on the autonomic nervous system, central nervous system, or the respiratory system. Increased

heart rate and carotid arterial blood flow was observed at 9 and 30 mg/kg, but no changes were noted in electrocardiograms (ECGs). Intestinal charcoal transit was slightly shortened, and urinary volume was decreased at 9 and 30 mg/kg. These minor changes were observed at systemic concentrations in excess of those expected following topical ocular administration of CSB-001.

In addition to systemic and ocular GLP safety data generated by Kringle and Claris, the safety of KP-100DS (drug substance dHGF) has been evaluated by Kringle in more than 185 subjects across seven completed or ongoing trials by multiple routes of administration including intravenous and intrathecal. An intrathecal formulation (KP-100IT) is in development by Kringle in Japan for amyotrophic lateral sclerosis (ALS) and acute spinal cord injury in ongoing Phase 2 and Phase 3 studies, respectively. Safety and systemic exposure of KP-100DS were assessed following single and multiple ascending dose intravenous administrations in renally and hepatically impaired subjects resulting in systemic exposure levels much greater than that predicted following topical ocular dosing in humans.

Collectively, these data suggest that dHGF administered topical ocularly in subjects with NK will be safe and efficacious in the healing of NK lesions (PED and ulcers). A detailed discussion of the clinical and nonclinical data relevant to CSB-001 is provided in the Investigator's Brochure.

Figure 1: Structure of dHGF



2. STUDY OBJECTIVES

2.1. 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, 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).

2.2. Other Objective

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 efficacy and safety data for CSB-001 in eyes with NK.

3. INVESTIGATIONAL PLAN

3.1. Study Overview

This study is designed to evaluate the safety and efficacy of CSB-001 ophthalmic solution 0.1% (CSB-001) compared to vehicle in subjects with stage 2 (persistent epithelial defect [PED]) or stage 3 (corneal ulcer) neurotrophic keratitis (NK).

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, Table 2.

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 2.

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.

3.2. Number of Subjects

Approximately 128 subjects (64 per treatment arm) will be randomized in the study to complete approximately 96 subjects (48 per treatment arm).

3.3. Study Eye Determination

In subjects with both eyes affected with stage 2 or 3 NK at screening, the worse eye as deemed by the investigator will be designated as the study eye and will be treated. If both eyes are equally affected, then the right eye will be designated the study eye and will be treated.

- The eye with the higher stage level assessed by 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 the study eye.
- Only the study eye will be randomized and treated

3.4. Treatment Assignment

Qualified subjects will be randomized at baseline in a 1:1 ratio:

- CSB-001 dosed QID in the study eye for 8 weeks
- Vehicle dosed QID in the study eye for 8 weeks

Randomization will be stratified by NK stage (2 or 3).

3.5. Initial Safety Phase

An initial safety phase is planned 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 following approximately seven days of dosing in the study eye. Subjects will continue to dose with test article and proceed with scheduled study visits unless a dose limiting event is identified. In the absence of an adverse event assessed as a dose limiting finding by the Medical Monitor during the initial safety phase, enrollment of the remaining subjects will commence.

In the event of an adverse event assessed as a dose limiting finding by the Medical Monitor that is also assessed as related to treatment by the investigator, the subject will be unmasked, and a determination will be made by the Sponsor regarding continued enrollment.

4. SUBJECT POPULATION

Approximately 128 subjects (64 in each arm) with stage 2 or 3 NK will be randomized to achieve 96 evaluable completers. Written informed consent will be obtained before initiation of any study procedures.

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study entry:

1. Subjects must be willing to read, understand, and give informed consent and sign and date the Informed Consent form before any study-related procedures are performed. The

Informed Consent form signed by subjects must have been approved by the IRB for the current study.

2. Male or female subjects 18 years of age or older.
3. Subjects with stage 2 (PED) or stage 3 (corneal ulcer) NK. Subjects with bilateral stage 2 or 3 NK may enroll in the study but only one eye (worse eye) will be selected as the study eye and be treated with test article.
4. Subjects with no clinical evidence of improvement in the PED or corneal ulcer within the 2 weeks prior to screening despite use of conventional non-surgical treatments for NK (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses [either silicone hydrogel or rigid gas permeable]) as determined by the investigator or referring physician's medical record.
    a. No clinical evidence of improvement is defined as no improvement and/or fluctuation in the aspects of the PED/ulcer that in the opinion of the investigator does not demonstrate progression towards resolution over the previous 2 weeks.
5. Subjects with 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 assessed using a cotton wisp.
6. Pinhole distance visual acuity score ≤ 75 ETDRS letters measured with a LogMAR chart, (≥ 0.2 LogMAR, 20/32 or worse Snellen or ≤ 0.625 decimal fraction) in the study eye.
7. Subjects must have the ability and willingness to comply with study procedures.

4.2. Exclusion Criteria

The exclusion criteria are designed to identify and exclude those subjects who may be at risk from treatment with dHGF or who may compromise the scientific integrity of the study. Subjects meeting any of the following criteria are ineligible for study entry. **Unless noted, the criteria below refer to the study eye.**

1. Any active ocular infection (bacterial, viral, fungal, or protozoal) or active ocular inflammation not related to NK in either eye in the opinion of the investigator. Infectious epithelial keratitis including herpetic keratitis (i.e., dendritic lesions or geographic ulcers) in either eye is excluded. Subjects on oral antibiotic at the time of screening are eligible but should continue the medication for the duration of the study.
2. Previous use of Oxervate in the study eye with the last administration within the past 2 months.
3. Any other ocular disease, except elevated intraocular pressure (i.e., ocular hypertension or glaucoma), that will require topical ocular treatment in the study eye over the course of the study.
4. Use of any other topical treatments other than the study medications provided by the Sponsor and allowed by the study protocol can be administered to the study eye over the course of the study. The following are exceptions:

   a. Allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator.
   b. Allowance for use of a non-preserved IOP-lowering topical ocular drop administered once-daily over the course of the study. Timolol is prohibited.

5. Schirmer's test without anesthesia ≤3 mm/5 minutes.
6. History of any ocular surgery (including laser procedures) within the 6 months before study enrollment with the exception of cataract surgery which is excluded within 3 months prior to screening. An exception to the preceding statements is allowed if the ocular surgery was considered the cause of the stage 2 or 3 NK.
7. Anticipated need for or planned ocular surgery over the course of the study.
8. Prior surgical procedure(s) for the treatment of NK (e.g., partial or complete tarsorrhaphy, conjunctival flap, etc.) within the past 2 months.
9. Anticipated need for amniotic membrane over the course of the study. Prior treatment with amniotic membrane (sutured or sutureless) within 6 weeks of enrollment or within 2 weeks after the membrane has disappeared or has been removed within the area of the PED or ulcer.
10. Prior treatment with autologous serum within 2 weeks of enrollment.
11. Subjects treated with Botox (botulinum toxin) injections to induce pharmacologic blepharoptosis within 90 days prior to enrollment in the study and the pharmacologic blepharoptosis has not resolved in the opinion of the investigator.
12. Anticipated need to use therapeutic contact lenses or contact lens wear for refractive correction over the course of the study. Use of any contact lens is not permitted during the study.
13. Anticipated need for punctal occlusion or punctal plugs over the course of the study. Subjects with non-dissolvable punctal plugs inserted prior to the study are eligible for enrollment provided that the plug is maintained during the study and promptly replaced if lost during the study. Short-term dissolvable plugs are allowed if inserted >2 weeks of screening. Long-term dissolvable plugs are allowed if inserted >4 months of screening.
14. Evidence of corneal ulceration involving the posterior third of the corneal stroma, corneal melting or perforation in the opinion of the investigator.
15. Presence or history of any ocular or systemic disorder or condition that might hinder the efficacy of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or could be judged by the investigator to be incompatible with the study visit schedule or conduct (e.g., progressive or degenerative corneal or retinal conditions other than NK or associated sequelae, uveitis, optic neuritis, poorly controlled diabetes, autoimmune disease, immunocompromised, systemic infection, neoplastic diseases). Keratoconus is excluded with the exception of subjects with a history of keratoconus who are post-transplant as the surgery may be the underlying cause of NK.

16. Any need for, or anticipated change in, the dose of systemic medications known to impair the function of the trigeminal nerve (e.g., antidepressants, neuroleptics, antipsychotics, and antihistamines) during the study period. These treatments are allowed during the study provided that they are initiated more than 30 days before study enrollment and are expected to remain stable throughout the course of the study treatment periods. Note that PRN use of these medications as a sleep aid is allowed.
17. Known hypersensitivity to any components of the test articles provided as part of the study, or procedural medications (e.g., fluorescein).
18. History of drug, medication, or alcohol abuse or addiction within the past 3 years.
19. Use of any investigational agent within 30 days of the Screening/Randomization Visit.
20. Participation in another clinical study at the same time as the present study.
21. Females of childbearing potential (those who are not surgically sterilized or postmenopausal for at least 1 year) will be excluded from participation in the study if they meet any one of the following conditions:
    a. are pregnant or,
    b. have a positive result on the urine pregnancy test at the Screening/Randomization Visit or,
    c. intend to become pregnant during the study treatment period or,
    d. are breast-feeding or,
    e. not willing to use highly effective birth control measures, such as: hormonal contraceptives –oral, implanted, transdermal, or injected and/or mechanical barrier methods –spermicide in conjunction with a barrier such as a condom or diaphragm or intrauterine device (IUD) during the entire course of and 30 days after the study treatment periods.

Note: Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

All females of childbearing potential will need to consent to a urine pregnancy test upon entering and exiting the study treatment period(s). Females of childbearing potential would need to agree to immediately inform the investigator if they became pregnant during the study. For non-sexually active females, abstinence could be regarded as an adequate method of birth control; however, if the subject becomes heterosexually active during the study treatment period, she will have to agree to use adequate birth control methods as defined above for the remainder of the study treatment period. Pregnancy is to be avoided in subjects or partners during the study treatment period and for the first month after completing the treatment with the investigational product.

Males with a partner of childbearing potential are eligible provided that he agrees to use adequate birth control methods such as a mechanical barrier protection and the partner agrees to use highly effective birth control measures, such as: hormonal contraceptives –oral, implanted,

transdermal, or injected and/or mechanical barrier methods –spermicide in conjunction with a barrier such as a condom or diaphragm or intrauterine device (IUD) during the course of and 30 days after the study treatment periods.

4.3. Concomitant Medications and Therapies

All prescription medications, over-the-counter drugs and significant non-drug therapies (including blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medication form.

- No topical ocular treatments other than the test articles provided for the study are allowed in the study eye over the course of the study. The following are exceptions:
  - Allowance for use of preservative-free antibiotic eye drops if prescribed by the investigator.
  - Allowance for use of a non-preserved IOP-lowering topical ocular drop administered once-daily over the course of the study. Timolol is prohibited.

  Subjects will be instructed to instill the antibiotic and/or IOP-lowering eye drops approximately 5 minutes after the test article is instilled.

  Topical anesthetic for tonometry and topical fluorescein required for protocol-defined study procedures are permitted.
- Artificial tears (gels or ointments) are not allowed in the study eye during the 8-week course of treatment in either the controlled or uncontrolled treatment phases. If used by the subject it must be recorded as a concomitant medication.
- Anti-viral eye drops are not allowed in the study eye during the study. Subjects requiring a topical anti-viral will be exited from the study and treated per investigator discretion.
- The use of therapeutic contact lenses (including silicone hydrogel and rigid gas permeable) or contact lens wear for refractive correction in the study eye during the study is prohibited.
- Non-dissolvable punctal plugs in the study eye is allowed during the study if present at the time of enrollment provided that these are maintained during the study and plugs promptly replaced if lost during the study. Insertion of dissolvable plugs in the study eye is prohibited during the study.
- Systemic medications known to impair the function of the trigeminal nerve (e.g., antidepressants, neuroleptics, antipsychotics, and antihistamines) are allowed during the study provided that they are initiated more than 30 days prior to study enrollment and remain stable throughout the course of the study. These medications used PRN as a sleep aid are allowed.
- Treatment with amniotic membrane (sutured or sutureless) during the study is prohibited.

5. STUDY TREATMENT

5.1. Subject Randomization and Treatment Assignment

Eligible subjects who meet study inclusion and exclusion criteria will be randomized in a 1:1 ratio to receive CSB-001 or vehicle. Randomization will be stratified by NK stage (2 or 3). One hundred and eight (128) subjects (64 in each treatment arm) are planned to be randomized to complete approximately 96 (48 in each treatment group).

This study will employ IBM Clinical Development (CD) for subject randomization and test article supply management. Prior to study initiation, the log in information and instruction for IBM CD will be provided to each site.

Subject randomization will be conducted centrally using an electronic randomization module (i.e., IBM CD). Site personnel will log into the system to randomize qualified subjects who meet inclusion / exclusion criteria. Subjects will be randomized to one of two treatment arms and will be assigned a unique subject identification number based on a computer-generated subject randomization scheme. Participants who meet all study eligibility criteria will be randomized at the Day 0 Visit of the controlled treatment phase.

Test article assignment will also be conducted centrally using IBM CD. Site personnel will log into the IBM CD system to obtain the kit code(s) for the subject at the time of each test article dispensation.

Both the subject randomization scheme and kit list will be generated by Statistical Analysis System programmers who will not be directly involved in study analysis.

5.2. Masking

The controlled treatment phase of this study will be double-masked. To minimize potential bias, study participants, investigators and other site staff, and the Sponsor will be masked to the treatment assignments.

The identity of the treatments will be concealed by the use of test articles that are identical in packaging and labeling, each with a unique kit code.

The uncontrolled treatment phase of this study is open-label and reserved for subjects randomized to vehicle in the controlled treatment phase whose cornea is not healed.

5.3. Description of Study Drug, Packaging and Labeling of Test Articles

5.3.1. Description of Study Drug

Test article refers to either CSB-001 or vehicle and is manufactured by Woodstock Sterile Solutions, Inc formerly known as Catalent Pharma Solutions, Woodstock IL. The active investigational product, CSB-001, is formulated as a sterile ophthalmic solution using the drug substance, human recombinant dHGF (5-amino acid deleted hepatocyte growth factor). CSB-001 drug product is a sterile, topical, ocular solution of dHGF in 20 mM citrate sodium, 0.05%, polysorbate 80 (PS80), and 200 mM trehalose at pH 6.0. It is a clear to slightly opalescent and colorless to light yellow solution, free from visible particulates.

The vehicle control product is identical to CSB-001 without the drug substance. The appearance of the vehicle is indistinguishable from that of the active investigational product, CSB-001.

5.3.2. Test Article Packaging, Labeling, Shipment and Storage

Test articles (CSB-001 and vehicle) will be contained in identical blow-fill-sterile (BFS) non-preserved single-dose vials that are packaged in identical foil pouches. Each foil pouch will contain 4 BFS vials, sufficient for four administrations per day. A 7-day supply of test article (i.e., 7 pouches each containing 4 BFS vials for a total of 28 BFS vials) will be packaged in a study kit. Study kits will be shipped to clinical sites to maintain a minimal test article inventory (i.e., two kits of each treatment) for randomization and test article dispensation at the Day 0 Visit of the controlled treatment phase.

Labeling will comply with country-specific requirements for investigational product. Each foil pouch (containing four BFS vials) and the outer kit carton (containing seven foil pouches) will be labelled at a minimum with the kit code number, study number, lot number, subject number, relevant Sponsor information and storage instruction. The label will also include the caution statement *Caution: New Drug-Limited by Federal (or United States) law to investigational use*. The BFS vials will be embossed with lot number and date of manufacture.

Test article must be kept within 2-8°C (36-47°F) during shipment and storage at the investigational site and following dispensation to the subject. Test article must be protected from light; subjects will be instructed to keep vials in the pouch and the pouch in the kit carton until the time of administration. Subjects will be provided with cooler bags to transport the test articles from the clinic to their residence and as needed when away from home.

Temperature indicators that can reliably indicate to the receiving party if the lower or upper temperature limits specified for storage (2-8° C) were exceeded in transit will be placed in each shipment. The staff at each receiving site will document the conditions of each shipment of study drug upon arrival, and immediately transfer the contents into secure, limited access, refrigerated storage locations. Study drug received by clinical sites that was not maintained at the specified temperature conditions in transit will be so identified and placed in quarantine, and the Sponsor notified.

5.4. Test Article Dispensation

Subjects meeting all inclusion and exclusion criteria and randomized into the study will be dispensed study drug at the Day 0 Visit of the controlled treatment phase. Two study drug kits will be dispensed at Day 0 (a primary kit and a back-up kit). Each kit will contain 28 BFS single-dose vials (for 7 days of QID dosing). Subjects will be instructed to use all the study drug from the primary kit before using drug from the back-up kit. Subjects will be instructed to store all test articles in the refrigerator or in the provided cooler bag when away from home until time of administration.

For subsequent dispensations after the Day 0 Visit (i.e., Week 1-7 visits), only one study drug kit will be dispensed. In situations where a subject may be late returning for a scheduled visit or have missed a scheduled visit and needs to dose with the back-up kit, the site will dispense another back-up kit when the subject returns for the follow-up visit. Subjects should have a primary kit and a back-up kit at all times.

The same process applies to test article dispensation for the open-label uncontrolled treatment phase.

5.5. Administration of Test Article

5.5.1. Controlled Treatment Phase

Test article (either CSB-001 or vehicle) will be administered topically onto the surface of the eye; one drop QID approximately every 4 hours for 8 weeks in the study eye starting at the Day 0 Controlled Phase Visit. At the Day 0 Visit, the first dose will be administered while the subject is at the clinic with site staff observing and training as needed.

Depending on the time of the Day 0 Visit, subjects may not be able to dose with all four doses on the initial day. Subjects will be instructed by the site staff to dose for the remainder of the Day 0 doses 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).

Depending on the time of the Week 8 Visit, the subject may not be able to dose with all four doses and dosing will be discontinued prior to the conduct of the ophthalmic study assessments at the Week 8 Visit.

Subjects will be instructed to use a new unused single-dose vial for each dosing and to not use an open vial which may still contain drug for subsequent dosing.

5.5.2. Uncontrolled Treatment Phase

Test article (CSB-001) will be administered as specified in Section 5.5.1 above. The initial day of dosing is at the Day 0 Uncontrolled Phase Visit.

5.6. Test Article Accountability

An accurate and current accounting of the dispensing and return of the test articles for each subject will be maintained on an ongoing basis by study site staff and will be recorded on the Test Article Accountability Record. Subjects will be required to keep used BFS vials and bring to the site at the follow-up visits which will be counted and recorded by site staff. All remaining unused test articles will be returned to the Sponsor in accordance with applicable laws and study site procedures after study completion/termination.

5.7. Unmasking

5.7.1. Unmasking of Subjects During the Controlled Treatment Phase

Non-responders, defined as subjects whose cornea is not healed at Week 8 or whose cornea is healed at Week 8 that is not sustained for two weeks until Week 10, will be unmasked at the Week 8 or 10 Visit, respectively. Those identified as randomized to vehicle at baseline are eligible to enter the uncontrolled treatment phase and receive an 8-week course of CSB-001 treatment. Those identified as randomized to active at baseline will exit the study and be managed per investigator discretion. See Schematic of Study Design, Figure 2.

5.7.2. Emergency Unmasking

Breaking the masking during the controlled treatment phase is expressly forbidden except in the event of a medical emergency where the identity of the study drug must be known to properly treat the subject. The decision to break the mask in an emergency situation remains the responsibility of the investigator which will not be delayed or refused by the Sponsor. When possible, the investigator should discuss emergency unmasking with the Medical Monitor prior to unmasking. The investigator should institute whatever treatment is deemed appropriate pending contact with the Sponsor/Medical Monitor to discuss unmasking.

The investigator should ensure that the code is broken only in accordance with the protocol. The investigator should promptly complete appropriate documentation to notify the Sponsor of the emergency unmasking and the reason for breaking the mask, which should be clearly documented in the participant's source documentation. An Adverse Event form will be completed and submitted to the Sponsor.

Emergency unmasking should only be performed by the investigator using the IBM CD system. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and an email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

An assessment will be done by the appropriate site personnel and the Sponsor after an emergency unmasking to determine if study treatment should be discontinued for a given subject.

5.8. Treatment Compliance

The investigator will remind subjects to administer the assigned test articles as instructed and emphasize that compliance is necessary for the subject's safety and the validity of the study. Subjects will be instructed that failing to comply with study procedures, such as repeatedly missing doses of test articles or not showing up for study visits, may result in their removal from the study at the discretion of the investigator in coordination with the Sponsor. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be reported by the subject and assessed by the investigator and/or study personnel at each visit and documented in the source document and eCRF. Additionally, subjects will be required to keep used BFS vials and return to the site at the follow-up visits to assist in monitoring compliance.

6. EVALUATIONS BY VISIT

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 below.

Note: Ocular procedures should be performed in the order listed for each visit ensuring that digital imaging is performed prior to any procedures that touches the eye and prior to instillation of any topical agents except for fluorescein.

6.1. Randomized, Double-Masked, Controlled Treatment Phase

Subjects will be randomized in a 1:1 ratio to the CSB-001 arm or to the vehicle arm stratified by NK stage 2 or 3.

An initial safety phase is planned 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 following approximately seven days of dosing in the study eye. In the absence of an adverse event assessed as a dose limiting finding, enrollment of the remaining subjects will commence.

The primary study endpoint is based on assessments at the Week 8 and 10 Visits; missed visits may impact the study analysis. Site personnel will apply due diligence to contact the subject to return for the Week 8 and 10 Visits.

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.

6.1.1. Day 0 Visit (Screening/Randomization; Baseline for Controlled Phase)

1. Review the study with the subject and obtain written informed consent for participation in the study
2. Assign the subject a unique subject ID
3. Record demographic data
4. Record medical history and concomitant medications/therapies (including systemic and ocular)
5. Perform logMAR pinhole distance VA OU
6. Perform slit-lamp exam OU (without fluorescein staining)
7. Note: Determine the study eye in subjects with bilateral stage 2 or 3 NK.
    - The eye with the higher stage level assessed by 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 the study eye.
    - Only the study eye will be randomized and treated
    - Document both the stage of NK and the study eye
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 ± 15 seconds after fluorescein

instillation. The second set of images will be collected 120 ± 15 seconds after fluorescein instillation.

- **In the event that fluorescein was instilled for another procedure performed on the same day prior to the digital imaging, wait at least 2 hours before re-instilling fluorescein and performing imaging as described above.**

9. Perform anterior segment OCT in the study eye (only at selected sites)
10. Perform NEI scale assessment of corneal staining via slit-lamp in the study eye (additional fluorescein may be instilled per investigator discretion)
11. Assess corneal sensitivity in the study eye using a cotton wisp
    - At sites with a Cochet-Bonnet aesthesiometer, assess and record corneal sensitivity with the Cochet-Bonnet device.
12. Perform Schirmer's test without anesthesia in the study eye
13. Perform IOP OU
14. Perform dilated fundus ophthalmoscopy OU
15. Perform urine pregnancy test if the subject is a female of childbearing potential
16. Review inclusion and exclusion criteria. If the subject meets all inclusion and exclusion criteria, randomize the subject using the IBM CD system.
17. Dispense 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

18. Administer the ocular tolerability questionnaire immediately after in-office administration of test article
19. Record any adverse events after test article instillation
20. 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 opened, 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.

6.1.2. Week 1 Visit (±2 day window)

Notes:

- The first 12 randomized subjects will be evaluated by the masked Medical Monitor for dose limiting safety findings. Each subject will be assessed within 3 days of the Week 1 Visit following approximately 7 days of dosing in the study eye. In the absence of an adverse event assessed as a dose limiting finding, enrollment of the remaining subjects will commence.
- For subjects in the initial safety phase (i.e., the first 12 randomized subjects), perform pinhole distance VA and slit-lamp exam in both eyes at the Week 1 Visit. For all other subjects, perform pinhole distance VA and slit-lamp in the study eye only at the Week 1 Visit.

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 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 ± 15 seconds after fluorescein instillation. The second set of images will be collected 120 ± 15 seconds after fluorescein instillation.

7. Perform investigator assessment of corneal healing and NEI scale assessment of corneal staining in the study eye (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.
    - 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 the 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 2 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.

6.1.3. Week 2 Visit (±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 ± 15 seconds after fluorescein instillation. The second set of images will be collected 120 ± 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)