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Sponsor: Surface Ophthalmics Inc.

07 October 2020 and 28 June 2022

Study Number C-200-001
Phase 2 Clinical Study Protocol, Amendment 01 including Statistical Analysis Plan

A Multicenter, Randomized, Double-masked, Dose-ranging Study To Compare the Ocular Safety, Tolerability, and Efficacy of SURF-200 Ophthalmic Solution (0.02% and 0.04% Betamethasone Sodium Phosphate) to Vehicle in Subjects with a Diagnosis of Dry Eye Disease and Experiencing an Episodic Flare Up

Original Protocol:	18 November 2019
Protocol Amendment 01:	07 October 2020
Initial IRB Approval:	15 October 2020
Statistical Analysis Plan:	28 June 2022

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LIST OF ABBREVIATIONS

Abbreviation or Acronym	Definition
AE	adverse event
BCVA	best-corrected visual acuity
BID	twice daily
BSP	betamethasone sodium phosphate
°C	degrees Celsius
CBD	cannabidiol
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CSCR	central serous chorioretinopathy
eCRF	electronic case report form
e.g.	exempli gratia; for example
ETDRS	early treatment diabetic retinopathy study
°F	degrees Fahrenheit
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
i.e.	id est; in other words
IOP	intraocular pressure
IRB	institutional review board
ITT	intent to treat
LASIK	laser-assisted in situ keratomileusis
IUD	intrauterine device
logMAR	log of the minimum angle of resolution
MedDRA®	Medical Dictionary for Regulatory Activities
Mm	Millimeter
mmHg	millimeters of mercury
No.	Number
NSAID	nonsteroidal anti-inflammatory drug
PP	per protocol
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SURF-200	Formulations of 0.02% and 0.04% betamethasone sodium phosphate ophthalmic solution
TBUT	tear break-up time
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
UNC DEMS	University of North Carolina Dry Eye Management Scale

Abbreviation or Acronym	Definition
US	United States
VA	visual acuity

1. STUDY OBJECTIVE

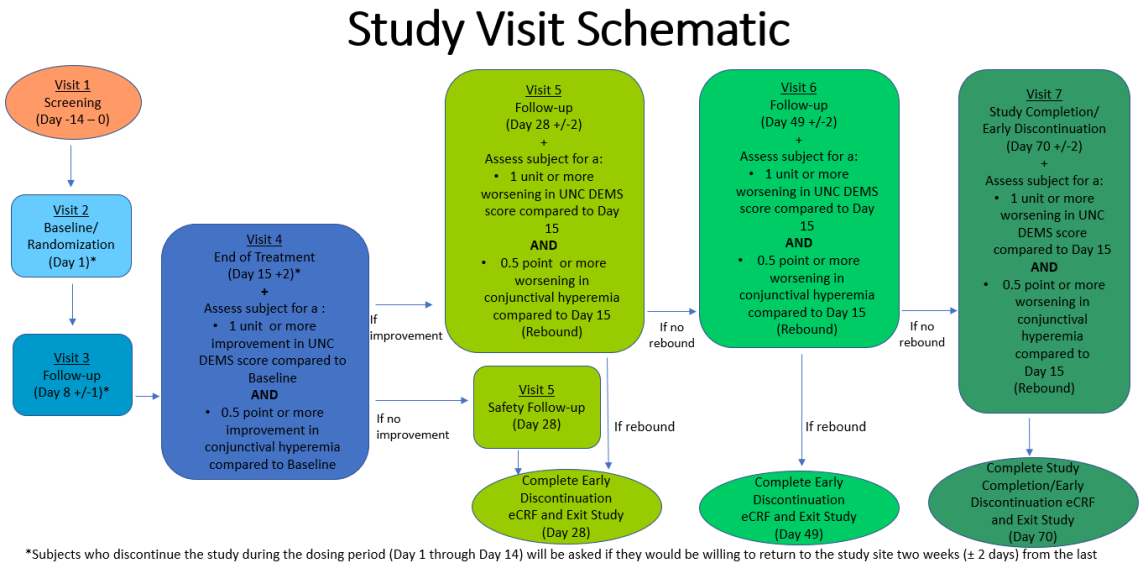
To evaluate the safety, tolerability, and efficacy of topical administration of SURF-200 ophthalmic solution (betamethasone sodium phosphate [BSP], 0.02% or 0.04%) compared to vehicle when dosed twice daily (BID) for 2 weeks and followed for an additional 8 weeks for assessment of rebound and safety in subjects with a diagnosis of Dry Eye Disease (DED) and experiencing an episodic flare up.

2. STUDY DESIGN

This study is a Phase 2, multicenter, randomized, double-masked, dose-ranging, vehicle-controlled, parallel-group clinical trial. Subjects 18 years of age and older with a diagnosis of dry eye disease and experiencing an episodic flare up who meet all study entry criteria will be enrolled. The investigator and his/her staff will not know which study medication the subject is receiving but will be able to determine this in the event of an emergency.

Prior to enrollment, the study will be discussed with prospective subjects and those wishing to enter will be asked to give written informed consent. Informed consent will be obtained prior to any study related procedures being performed. Once informed consent has been obtained, the subjects will be questioned regarding their medical history to determine whether or not they are in satisfactory health to enter the study and to determine if they meet the specific entry criteria.

There will be a total of 7 study visits:
Screening Visit 1 (Day -14 to Day 0), Baseline/Randomization Visit 2 (Day 1), Visit 3 (Day 8), End of Treatment Visit 4 (Day 15), Visit 5 (Day 28), Visit 6 (Day 49) and Study Completion/Early Discontinuation Visit 7 (Day 70).



*Subjects who discontinue the study during the dosing period (Day 1 through Day 14) will be asked if they would be willing to return to the study site two weeks (± 2 days) from the last dose of study drug for the Visit 7/Early Discontinuation Visit, for subject safety. If the subject is willing to return in two weeks for the Visit 7/Early Discontinuation Visit, the subject will be discontinued from the study following the completion of the Visit 7/Early Discontinuation Visit. If the subject is not willing to return in two weeks for the Visit 7/Early Discontinuation Visit, the subject will be discontinued from the study at the current visit and all Visit 7/Early Discontinuation assessments will be performed during the current visit.

Screening (Day -14 to Day 0), Randomization (Day 1), and Dosing Phase (Day 1 to Day 14):

During the screening phase of the study, subjects who meet all inclusion and none of the exclusion criteria will be randomized in a 1:1:1 ratio: 40 subjects in the 0.02% BSP group, 40 subjects in the 0.04% BSP group, and 40 subjects in the vehicle group. During the dosing phase (Day 1 to Day 14), subjects will instill study drug BID for 14 days. Subjects will receive instructions for dosing at home and for completing a Study Drug Dosing Diary with Drop Comfort Questionnaire during the study dosing phase (Day 1 to Day 14). Subjects (or their caregivers) will be instructed to store the study drug at room temperature (15°- 25°C; 59° - 77°F), to protect the study drug from light and to not freeze the study drug, as well as to instill 2 doses (preferably 8-12 hours apart) every day for 14 days in the study eye and the fellow eye, if applicable. The fellow eye can only be dosed if it was determined by the investigator at baseline that the fellow eye requires relief of dry eye symptoms as well. The fellow eye must follow the same dosing regimen as the study eye.

Visit 3 (Day 8)

Subjects will be assessed for safety and efficacy assessments.

Visit 4 (Day 15): Improvement

Subjects who achieve a 1 unit or better improvement in University of North Carolina (UNC) Dry Eye Management Scale (DEMS) score and a 0.5 point or better improvement in conjunctival hyperemia at Visit 4 (Day 15) when compared to their baseline scores will then be followed for 8 weeks during the evaluation phase (Day 15 to Day 70) to assess for a rebound and safety.

Rebound Assessments at Visit 5 (Day 28), Visit 6 (Day 49), and Visit 7 (Day 70)

Rebound is assessed at Visit 5 (Day 28), Visit 6 (Day 49) and Visit 7 (Day 70) when compared to Visit 4 (Day 15) as a 1 unit or more worsening in UNC DEMS score and a 0.5 point or more worsening in conjunctival hyperemia. Subjects who meet this definition of having a rebound will complete the current visit (either Visit 5 [Day 28], Visit 6 [Day 49] or Visit 7 [Day 70]) and then be discontinued from the study prior to receiving another possible treatment.

Visit 4 (Day 15): No Improvement - Early Discontinuation

Subjects who do not achieve a 1 unit or better improvement in UNC DEMS score and a 0.5 point or better improvement in conjunctival hyperemia at Visit 4 (Day 15) when compared to their baseline score will complete the Early Discontinuation Visit (Visit 7).

Subjects will be instructed to bring all their study drug (used and unused) and subject diaries with them to Visit 3 (Day 8) for review with site staff, and to return their study drug (used and unused) and subject diaries at Visit 4 (Day 15).

Subjects' safety will be evaluated throughout the study. The safety parameters to be assessed are the incidence, severity, and relationship of adverse events (AEs) and serious adverse events (SAEs), discontinuations due to AEs, changes in visual acuity (VA) and intraocular pressure (IOP), and biomicroscopic and ophthalmoscopic findings in treated eyes.

Efficacy will be assessed as follows: All analyses will be done descriptively. No confirmatory statistical testing will be performed, but exploratory statistical tests may be used to evaluate the efficacy parameters. Data for the study eye will be used for all efficacy analyses.

Primary Efficacy Analysis:

The primary efficacy analysis planned is listed below. Each active treatment group (0.02% and 0.04% BSP) will be independently compared to the Vehicle group. As this is a Phase 2 study, no superiority claims are being tested; therefore, no adjustments will be made for multiple comparisons. Comparisons will be made with a two-sided Fisher's exact test with an alpha-level of 0.05.

1. The proportion of subjects with clinically significant improvement from baseline in UNC DEMS score at Visit 3 (Day 8) will be summarized for each treatment group. A clinically significant improvement is defined as a minimum reduction in UNC DEMS score of 1 unit or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures.

Secondary Efficacy Analyses:

The two secondary efficacy analyses planned are listed below.

1. The proportion of subjects with clinically significant improvement from baseline in UNC DEMS score at Visit 4 (Day 15) will be summarized for each treatment group. A clinically significant improvement is defined as a minimum reduction in UNC DEMS score of 1 unit or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 4 (Day 15) will be treated as failures.

2. The proportion of subjects with clinically significant improvement from baseline in conjunctival hyperemia (using a consistent light source, examiner and exam room from visit to visit) in the study eye at Visit 3 (Day 8) will be summarized for each treatment group. A clinically significant improvement is defined as an improvement of 0.5 points or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures.

Biomicroscopy and ophthalmoscopy study examinations should be performed by the same board-certified ophthalmologist or a board-certified or state licensed optometrist (that would allow them legally to diagnose and treat patients independently) from visit to visit. All other ratings and procedures should be performed by the same examiner from visit to visit whenever possible.

Additional exams may be scheduled as necessary to ensure the safety of the subjects during the study period.

3. STUDY CONDUCT

Initiation of this study requires acceptance and approval by a qualified, properly constituted Institutional Review Board (IRB). Approval of the study by the governing IRB will be secured prior to the initiation of the study at each site and a copy of the approval provided to the study Sponsor or designee. The IRB must function in compliance with 21 CFR, Part 56 of the US Food and Drug Administration's (FDA) Code of Federal Regulations (CFR).

This study will be conducted in compliance with the protocol approved by the IRB, and according to Good Clinical Practice (GCP) standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such cases, the deviation will be reported, in writing, to the IRB and the Sponsor or designee as soon as possible.

4. STUDY POPULATION

The study population will include subjects who are ≥18 years of age with a clinical diagnosis of dry eye disease and experiencing an episodic flare up. Criteria for the diagnosis must include the following:

a. Minimum score of greater than or equal to 5 but less than or equal to 9, as assessed by the UNC DEMS.
b. Conjunctival hyperemia score greater than or equal to 2 in the study eye when using the conjunctival hyperemia reference photos.
c. Schirmer's Tear Test score (with anesthesia) greater than 1 mm but less than or equal to 12 mm in the study eye.

Approximately 120 subjects at multiple sites located in the United States (US) will participate in the study in a 1:1:1 ratio: 40 subjects in the 0.02% BSP group, 40 subjects in the 0.04% BSP group and 40 subjects in the vehicle group.

4.1. Inclusion Criteria

The following are inclusion criteria for prospective study subjects to be confirmed at Screening Visit 1 (Day -14 to Day 0) and again at Baseline/Randomization Visit 2 (Day 1) prior to randomization:

1. Volunteers 18 years of age and older who have a diagnosis of dry eye disease and experiencing an episodic flare up. Criteria for the diagnosis must include the following:
    a. UNC DEMS score of greater than or equal to 5 but less than or equal to 9
    b. Conjunctival hyperemia score of greater than or equal to 2 in the study eye when using the conjunctival hyperemia reference photos
    c. Schirmer's Tear Test score (with anesthesia) greater than 1 mm but less than or equal to 12 mm in the study eye

2. Subjects must be able to understand and sign the Informed Consent Form (ICF).

3. Female subjects of childbearing potential must agree to and submit a negative urine pregnancy test before any study-specific procedures are performed. The subjects must be using and continue to use a suitable method of contraception for the duration of the study: spermicide with barrier, oral contraceptive, transdermal contraceptive, injectable or implantable contraceptive, intrauterine device (IUD), abstinence or surgical sterilization of a partner. If a subject is not of childbearing potential (e.g., has been postmenopausal for at least 12 months or is premenarchal, or has undergone a hysterectomy, bilateral oophorectomy or a bilateral tubal ligation), a urine pregnancy test and use of a suitable method of contraception for the duration of the study will not be required.

4. Subjects must have a best-corrected visual acuity (BCVA) of at least +1.0 log of the minimum angle of resolution (logMAR) (Snellen equivalent of 20/200) in the non-study eye (fellow eye).

5. Subjects must have an IOP of >8 mmHg and ≤22 mmHg in the study eye.

6. Subjects who are on Restasis, Xiidra or other cyclosporine ophthalmic eye drops must be on a stable dose for at least 4 months prior to Screening Visit 1 (Day -14 to Day 0) and remain compliant with the use of these medications throughout the duration of this study.

7. Subjects who are on artificial tears, oral antihistamine, beta blockers and diuretics must be on a stable dose for at least 1 month prior to Screening Visit 1 (Day -14 to Day 0) and remain compliant with the use of these medications throughout the duration of this study.

8. Subjects must be willing and able to attend all study visits and follow all instructions.

9. Subjects must be able to self-instill the study drug (if unable, a caregiver must be available to instill all doses of the study drug).

10. Have a history of use or desire to use an eye drop for dry eye symptoms for longer than the past 6 months.

4.2. Exclusion Criteria

The following are exclusion criteria for prospective study subjects to be confirmed at Visit 1 - Screening (Day -14 to Day 0) and again at Baseline/Randomization Visit 2 (Day 1) prior to randomization:

1. Females who are pregnant or nursing or planning to become pregnant during the study. Females of childbearing potential (not surgically sterilized or postmenopausal) may not participate in the study if they do not agree to use adequate birth control methods for the duration of the study.

2. Use of contact lenses in either eye during the study. Contact lens wear must have been discontinued at least 2 weeks prior to Baseline/Randomization Visit 2 (Day 1).

3. Use of corticosteroids or nonsteroidal anti-inflammatory agents (NSAID) (except oral doses of aspirin at 81 mg/day or lower) for 2 weeks prior to the initiation of study drug at Baseline/Randomization Visit 2 (Day 1) and for the remainder of the study.

4. Inhaled, ingested, sublingual, transdermal or topical products containing marijuana, tetrahydrocannabinol (THC) or cannabidiol (CBD) at least 7 days prior to the first dose of study drug at Baseline/Randomization Visit 2 (Day 1) and for the remainder of the study.

5. Presence or history of treatment with systemic immunosuppressive or chemotherapeutic agents.

6. History of high IOP response to steroids.

7. Participated in an ophthalmic investigational product clinical trial within 30 days of Screening Visit 1 (Day -14 to Day 0).

8. Active collagen vascular disorder or autoimmune disease.

9. A condition or a situation, which in the investigator's opinion may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

10. Known hypersensitivity to any component of the study drug or procedural medications.

11. Known hypersensitivity to steroids.

12. Any active corneal epithelial/stromal pathology noted in the study eye at Screening Visit 1 (Day -14 to Day 0).

13. Any history of corneal surgery in the study eye (including corneal crosslinking, radial keratotomy, corneal transplant, or LASIK).

14. Any ocular surgery in the study eye within the past year.

15. Subject has punctal occlusion with any modality or a change in punctal plug status in either eye within the 3 months prior to Screening Visit 1 (Day -14 to Day 0).

16. Subject has a history of glaucoma.

17. Subject has a history of herpes simplex infection in either eye.

18. Subject has active corneal, conjunctival or canalicular pathology (including ocular infection [bacterial, viral or fungal]) in either eye. Specifically, active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and mycobacterial infection of either eye and fungal diseases of the ocular structures (such as fungal keratitis).

19. Subject has thinning of the cornea or sclera in the study eye.

20. Subject has active anterior blepharitis in the study eye.

21. Subject has a history of uveitis in the study eye.

22. Subject is suffering from alcohol and/or drug abuse.

23. Subject has tested positive for the COVID-19 virus within 30 days prior to Screening Visit 1 (Day -14 to Day 0).

24. Subject has previously received treatment in this study protocol.

25. Subject is taking a medication, that in the opinion of the investigator, might interfere with the study parameters.

5. STUDY DRUG/INSTRUCTIONS FOR USE AND ADMINISTRATION

The study drug will be masked, packaged and labeled in a manner consistent with the study design. The Sponsor or designee shall provide the packaging of and labeling of the study drug. The study drug will be identified as a new drug, limited by Federal law to investigational use, manufactured and packaged for Surface Pharmaceuticals. The study number, unique kit number, Sponsor information, storage instructions and dosing instructions will be identified on the label. Fields for the site staff to write-in the subject number to which the study drug kit will be assigned as well as the subject's unique randomization number will also be present on the label.

Subjects will be randomly assigned to receive masked study drug (either 0.02% or 0.04% BSP ophthalmic solution or vehicle) for 14 days BID. Subjects will receive instructions for dosing at home and for completing a dosing diary with a drop comfort questionnaire during the study dosing phase (Day -1 to Day 14).

During the 14-day dosing period, a total of 28 doses (2 doses each day, once in the morning and once in the evening, preferably 8-12 hours apart) will be instilled in the study eye and, if applicable, in the fellow eye by the subject (or their caregiver).

6. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindications: Betamethasone sodium phosphate (BSP), as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

***Warnings and Precautions*:** Ocular adverse reactions which may occur with SURF-200 based on marketed ophthalmic corticosteroids include the following:

- Prolonged intensive use of corticosteroids may result in IOP increase, glaucoma with damage to the optic nerve, posterior subcapsular cataracts, thinning of the globe and eventual perforation, secondary ocular infection, reduced visual acuity and visual field defects, mydriasis, ptosis, epithelial punctate keratitis, and corneal calcification may occur.

- Delayed healing - The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids.
- Bacterial infections - Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Viral infections - Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections - Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

***Special Warnings and Precautions for Use*:**

- Topical corticosteroids should never be given for an undiagnosed red eye as inappropriate use is potentially blinding.
- Persistent visual disturbance may be reported with systemic and topical corticosteroid use. Persistent symptoms such as blurred vision or other visual disturbances should be evaluated for possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

***Undesirable Effects*:**

- Hypersensitivity reactions usually of the delayed type, leading to irritation, burning, stinging, itching and dermatitis.
- Corneal calcification has been reported very rarely in association with the use of phosphate-containing eye drops in some patients with significantly damaged corneas.

***Overdose*:** Long term intensive topical use may lead to ocular corticosteroid specific class effects. Oral ingestion of the contents of a single-dose container of SURF-200 is unlikely to lead to any serious adverse effects.

***Drug-Drug Interactions*:** No topical ophthalmic drug-drug interactions are known for SURF-200. Corticosteroids (including betamethasone sodium phosphate) are metabolized by CYP3A4. Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects. Coadministration with other strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased exposures of corticosteroids and therefore the potential for increased risk of systemic corticosteroid side effects. (Celestone Soluspan PI 2018).

***Effects on Ability to Drive and Use Machines*:** SURF-200 may cause transient blurring of vision on instillation into the eye. Patients should be warned not to drive or operate hazardous machinery unless vision is clear.

7. CONCOMITANT MEDICATIONS

Disallowed medications include corticosteroids and NSAIDs (except oral doses of aspirin at 81 mg/day or lower) within 2 weeks of the initiation of study drug at Baseline/Randomization Visit 2 (Day 1) and for the remainder of the study. Stable use of inhaled and nasal corticosteroids and topical dermal steroids (except on the eyelids) are allowed.

Disallowed medications also include inhaled, ingested, sublingual, transdermal or topical products containing marijuana, tetrahydrocannabinol (THC) or cannabidiol (CBD) within 7 days prior of the first dose of study drug at Baseline/Randomization Visit 2 (Day 1) and for the remainder of the study.

Administration of any concomitant medication must be reported in the appropriate section of the source documents and Concomitant Medications Case Report Form.

A prohibited drug may be administered in an emergency situation if the subject's safety is in jeopardy. If possible, the sponsor should be consulted prior to administration of the prohibited drug (if not feasible, then as soon as possible afterwards) to determine whether the subject may continue in the study.

Concomitant medications (both prescription and nonprescription [including over the counter medicine, vitamins, supplements, and herbal supplements]), taken within 3 months prior to Screening Visit 1 (Day -14 to Day 0) will be recorded in the source documents and entered on the appropriate electronic case report form (eCRF). Doses of concomitant medications should remain stable, if possible, during the study. All concomitant medications taken throughout the course of the study, including any medications required to treat AEs or concomitant illnesses and any changes in concurrent medications, will also be recorded in the source documents and entered on the appropriate eCRF. Concomitant medications used for ocular exams, including but not limited to Fluress®, proparacaine, benoxinate or fluorescein, will not be collected.

8. CLINICAL ASSESSMENTS/EXAMINATION PROCEDURES

Assessments Completed by Subjects:

UNC DEMS Questionnaire: The UNC DEMS will be completed by subjects at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 1, prior to randomization) if Visit 2 is >5 days following Visit 1. The UNC DEMS will also be completed by subjects at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70).

Dosing Diary with Drop Comfort Questionnaire: Subjects will be given a Dosing Diary with Drop Comfort Questionnaire to record study drug dose instillation dates and times for each dose, as well as to record their responses to the Drop Comfort Questionnaire twice weekly during the dosing period (Day 1 to Day 14).

Assessments Completed by Investigators:

Best-Corrected Visual Acuity (BCVA): BCVA will be performed in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 1, prior to randomization) if Visit 2 is >5 days following Visit 1. BCVA will also be performed in treated eyes at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70). Log of the minimum angle of resolution (logMAR) score using ETDRS (Early Treatment Diabetic Retinopathy Study) chart will be used to measure BCVA. Performing a pinhole test is allowed as long as its use remains consistent for the same subject throughout all study visits.

Biomicroscopy: Slit lamp biomicroscopy will be performed to observe the overall health of the eye, including the lid/lashes, conjunctiva, cornea, anterior chamber, iris, and lens. This will be performed in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. Slit lamp biomicroscopy will also be performed in treated eyes at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70).

Ophthalmoscopy: An ophthalmoscopy examination will be performed in both eyes at Screening Visit 1 (Day -14 to Day 0) and in treated eyes at End of Treatment Visit 4 (Day 15). If anesthesia is used to perform the ophthalmoscopy examination, symptom assessments will be completed first before anesthesia administration or dilation.

***Intraocular Pressure (IOP)*:** IOP will be measured in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. IOP will also be measured in treated eyes at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70).

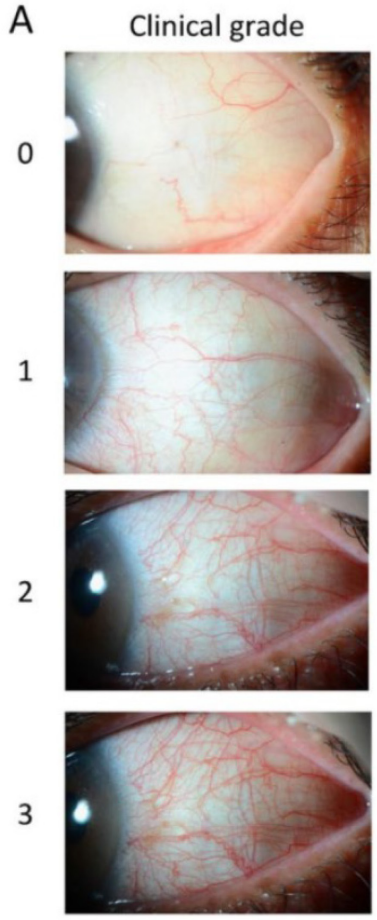
Conjunctival Hyperemia Assessment: Conjunctival hyperemia will be measured in both eyes at Screening Visit 1 (Day -14 to Day 0) and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. Hyperemia will be measured in treated eye(s) at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70). Clinical grade conjunctival hyperemia reference photos will be used to confirm the hyperemia eligibility score of 2.0 or greater and any improvement or worsening in conjunctival hyperemia from visit to visit.

Conjunctival hyperemia will be graded by the investigator using the following scale:

Grade	Description
0	(none: no hyperemia of the bulbar conjunctiva)
0.5	(Grade 0 plus dilation of at least a couple of conjunctival blood vessels but less than Grade 1)
1	(mild: the dilation of a few conjunctival blood vessels)
1.5	(Grade 1 plus dilation of some conjunctival blood vessels but less than Grade 2)
2	(moderate: the dilation of several conjunctival blood vessels)
2.5	(Grade 2 plus dilation of many conjunctival blood vessels but less than Grade 3)
3	(severe: the abundant and overwhelming dilation of many conjunctival blood vessels)

Conjunctival Hyperemia Reference Photos

(Sakamoto, E, et al (2019). "Evaluation of offset of conjunctival hyperemia induced by a Rho-kinase inhibitor; 0.4% Ripasudil ophthalmic solution clinical trial." Scientific Reports 9(1):3755, Figure 5.)



***Tear Break-up Time (TBUT)*:** TBUT will be conducted in both eyes at Screening Visit 1 (Day -14 to Day 0) and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. TBUT will also be measured in the treated eye(s) at Visit 3 (Day 8) through Study Completion/Early Withdrawal Visit 7 (Day 70).

***Sodium Fluorescein Corneal Staining*:** Sodium fluorescein staining will be conducted in both eyes at Screening Visit 1 (Day -14 to Day 0), and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. Corneal staining will be measured in treated eye(s) at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70) to assess corneal integrity.

***Conjunctival Staining*:** Conjunctival staining will be conducted in both eyes at Screening Visit 1 (Day -14 to Day 0), and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. Conjunctival staining will be measured in treated eye(s) at Visit 3 (Day 8) through Study Completion/Early Discontinuation Visit 7 (Day 70) to assess conjunctival integrity. The method of choice (i.e., dye) for conjunctival staining will be at the investigator's discretion. However, the same method of conjunctival staining should be applied throughout the study.

***Schirmer Tear Test*:** Schirmer tear tests will be conducted with anesthesia in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 1) if Visit 2 is >5 days following Visit 1. Schirmer tear tests (with anesthesia) will also be conducted in treated eye(s) at Visit 3 (Day 7) through Study Completion/Early Discontinuation Visit 7 (Day 70) to assess aqueous production.

Adverse Events and Concomitant Medications: At each study visit, subjects will be queried for new adverse events and, if applicable, previously unresolved adverse events. Also, concomitant medications will be documented.

Diary: At Visit 2 through Visit 4 (Day 1 through Day 15), subjects' Dosing Diaries will be reviewed and compliance with study drug dosing and completion of the Drop Comfort Questionnaire will be evaluated.

Biomicroscopy and ophthalmoscopy study examinations should be performed by the same board-certified ophthalmologist or a board-certified or state licensed optometrist (that would allow them legally to diagnose and treat patients independently) from visit to visit. All other ratings and procedures should be performed by the same examiner from visit to visit whenever possible.

9. ADVERSE EVENTS

Throughout the course of the study, the investigator must remain alert to possible adverse events or untoward findings. If adverse events occur, the first concern will be the safety of the subject. Appropriate medical intervention will be provided by the investigator.

Adverse Event (AE) Definition: An AE is any untoward medical occurrence associated with the use of a study drug in a clinical investigation subject, whether or not considered related to the study drug.

Adverse Event Reporting Period: The AE reporting period for this trial begins upon signing the ICF and ends at the completion of the subjects' final study visit exam. All AEs reported by the subject during the course of the study, or elicited by questions from the investigator, or noted as a result of procedures carried out on the subject, during the AE-reporting period must be recorded by site staff in the source documents and on the AE eCRF, whether or not the event is considered related to the study drug. In addition, any known untoward event that occurs subsequent to the AE reporting period that the investigator assesses as related to the study drug should also be reported as an AE.

Serious Adverse Event (SAE) Definition: A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening or immediately sight-threatening in a treated eye(s)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

SAE Reporting: SAEs must be immediately reported (within 24 hours of awareness of the event) to designated contract research organization (CRO) and will be clearly documented in the source documents and on the appropriate AE eCRF and SAE Report Form. The investigator must also notify the IRB of any SAEs, according to the IRB's guidelines.

Pre-existing Conditions: In this trial, a pre-existing condition (i.e., a disorder present before the AE-reporting period started and noted on the Systemic and/or Ocular Medical History Forms) should not be reported as an AE unless the condition worsens or episodes increase in frequency or severity during the AE-reporting period.

***BCVA*:** A worsening of 3 lines or more in log of the minimum angle of resolution (logMAR) score in the study eye from baseline or any prior visit should be captured in the source documents and on the appropriate eCRF as an AE.

IOP: An increase from baseline or any prior study visit of 10 mmHg in IOP in the study eye should be captured in the source documents and on the appropriate eCRF as an AE. An IOP of 30 mmHg or higher will be reported as an SAE.

Biomicroscopy: Slit lamp biomicroscopy will be performed to observe the overall health of the eye, including the lid/lashes, conjunctiva, cornea, anterior chamber, iris, and lens. Any biomicroscopy observations noted prior to Screening (Visit 1) should be recorded as ocular medical history. Any treatment-emergent findings (i.e., findings that were not present prior to treatment or a worsening relative to the pretreatment baseline) should be recorded as an AE.

Ophthalmoscopy: A new finding or a significant worsening (2 units or more) from baseline should be recorded as an AE.

AE Considerations: Additional exams may be scheduled as necessary to ensure the safety of the subjects during the study period. Subjects discontinued due to an AE should be seen for post-study follow-up visits, as needed. Adverse events considered related to study drug that have not resolved or stabilized by the final study visit will be followed during post-study follow-up visits at the discretion of the investigator until the incident has resolved or stabilized and will be documented in the source documents and AE eCRF. Where appropriate, additional written reports and documentation will be provided. Adverse events considered not related to study drug that have not resolved or stabilized by the final study visit will be noted as ongoing in the eCRF, followed at the discretion of the investigator, and recorded in the source documents.

Pregnancy: Although pregnancy is not considered an AE, any complication related to pregnancy would be considered an AE and recorded in the source documents and, if applicable, on the AE eCRF. If an SAE is associated with the pregnancy, the SAE should be reported on the SAE Report Form.

10. STATISTICAL ANALYSES

10.1. Randomization, Stratification, and Masking

Eligible subjects will be randomly assigned to each of the SURF-200 and vehicle groups in a 1:1:1 ratio according to a validated SAS® computer-generated central randomization schedule. The randomization schedule contains the coded treatment assignments for each randomization number. The randomization plan will be based on the study design, number of treatment groups and number of sites.

The randomization is generated by an un-masked statistician who is not affiliated with the study. The randomization plan will be based on the study design, number of treatment groups, and number of sites. It is shared with the Sponsor's designee responsible for final clinical packaging and labeling to allow for proper packaging and labeling of the study drug supply. Access to the randomization code will be strictly controlled according to the Sponsor designee's Standard Operating Procedures (SOPs).

The randomization is not unmasked until the study is complete and the database is locked. The Sponsor will confirm in writing that there are no regulatory or quality issues which preclude the unmasking of the study.

Unmasking of the randomization code prior to study completion due to a medical emergency will be managed in accordance with the Sponsor designee's SOP. All unmasked cases will be fully documented. Otherwise, the study mask will remain intact.

In this double-masked study, the investigator and his/her study staff, the subject (including caregiver, if applicable) and Sponsor/designee (other than as stated above) are masked to the identity of the study drug.

10.2. Efficacy and Safety Variables

Primary Efficacy Endpoint:

- The primary endpoint is the proportion of subjects with clinically significant improvement from baseline in UNC DEMS score at Visit 3 (Day 8). A clinically significant improvement is defined as a minimum reduction in UNC DEMS score of 1 unit or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures.

Secondary Efficacy Endpoints:

- The proportion of subjects with clinically significant improvement from baseline in UNC DEMS score at Visit 4 (Day 15). A clinically significant improvement is defined as a minimum reduction in UNC DEMS score of 1 unit or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 4 (Day 15) will be treated as failures.
- The proportion of subjects with clinically significant improvement from baseline in conjunctival hyperemia (using a consistent light source, examiner and exam room from visit to visit) in the study eye at Visit 3 (Day 8). A clinically significant improvement is defined

as an improvement of 0.5 points or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures.

Safety Variables: AEs (including SAEs), BCVA, IOP, biomicroscopic and ophthalmoscopic findings.

10.3. Analysis Populations

Intent-to-Treat Population: The Intent-to-Treat (ITT) population includes all randomized subjects regardless of whether post-baseline measures are collected, or study drug is received. Subjects in the ITT population will be analyzed in the treatment group to which they were assigned by the randomization schedule, regardless of which study drug they receive.

Per Protocol Population: The per-protocol (PP) population includes all subjects who received at least one dose of study drug and had no significant protocol deviations.

Safety Population: The safety population includes all subjects who receive at least 1 dose of the study drug. Subjects in the safety population will be analyzed in the treatment group for the study drug they received.

10.4. Data Handling: Handling of Missing Data

All missing data will generally not be imputed unless otherwise specified. For subjects who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All study discontinuations will be included in all analyses up to the time of study discontinuation.

For the classification of treatment emergent adverse events (TEAEs) and concomitant medications, the following will be applied in case of missing/incomplete dates:

- If all dates/times (start and stop) are missing, the event/medication will automatically be classified as a TEAE/concomitant medication.
- For AE/medication with a missing start date/time, if the event end date/time is prior to first study drug administration, the event will not be classified as a TEAE/concomitant medication, as applicable.
- If only the AE start year/medication end year is present and is the same or is after the first study drug administration year unit, the event/medication will be classified as a TEAE/concomitant medication, as applicable.
- If the AE start month and year/medication end month and year are present and are the same or after the first study drug administration month and year units, the event/medication will be classified as a TEAE/concomitant medication, as applicable.

10.5. Statistical Methods: General Considerations

All final statistical analyses will be performed after the study database has been locked, unmasked, and released for statistical analysis. All tables, statistical analyses, figures, and subject data listings will be generated using SAS® Version 9.4 or later (SAS Institute Inc., Cary, North Carolina, United States of America).

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by treatment group, subject number and assessment visit, as appropriate.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations (n), mean, standard deviation (SD), median, minimum and maximum values. The minimum and maximum values will be presented to the same number of decimal places as the eCRF or laboratory reported data; mean, SD, and median will be presented to one more decimal place than the source data.

Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Percentages will be rounded to one decimal place, with the denominator being the number of patients in the relevant population, unless otherwise stated.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the figures and listings.

It should be noted that in this study the analysis unit is subject. When data from both eyes are available, data will not be pooled together for the analysis because eyes from the same subject are not independent samples. Statistical analysis generally requires independent samples. Each subject has a designated study eye as per the protocol. Therefore, separate analysis will be conducted for study eye and fellow eye as appropriate.

All confidence intervals (CIs) of the parameter estimates will be two-sided and at the significance level of 0.05 unless otherwise stated.

All data summaries and data listings will use the nominal visit names as captured in the eCRF and as per the protocol schedule of visits. Derived visit windows will not be used for the data analysis. For all ‘by visit’ summary analyses of efficacy and safety endpoints, if a subject has an early discontinuation before Visit 6/Day 84, the data from the early discontinuation visit will be included in Visit 6/Day 84 assessment. If a subject has an early discontinuation after Visit 6/Day 84 but before Visit 7/Day 98, the data from the early discontinuation visit will be included in Visit 7/Day 98 assessment.

10.6. General Derived and Transformed Data

Age, in completed years, at informed consent date will be defined as: Age (years) = integer value (Date of Informed Consent – Date of Birth + 1) / 365.25).

Study day will be calculated using the first dosing date as the reference date. If the date of interest occurs on or after the first dosing date, then study day will be calculated as (date of interest – date of first dosing) + 1. If the date of interest occurs prior to the first dosing date, then study day will be calculated as (date of interest – date of first dosing). The day of the first dosing will be identified as Study Day 1 according to Clinical Data Interchange Standards Consortium (CDISC) standard. If a subject is dosed but dosing dates are missing, then the randomization date will be used as the first dosing date for the calculation of study day. Data listings will present study days in addition

to assessment dates, where applicable. As per above, all data summaries and data listings will use the nominal visit names as captured in the CRF and as per the protocol schedule of visits. The calculated study day as per CDISC will only be used in data listings to indicate the distance of an event from the dosing day.

Baseline will be defined as the last available, non-missing observation prior to the first dosing time with study drug, unless specifically mentioned otherwise. When baseline is derived, all data before the first dosing with study drug, including unscheduled visits before the first dosing with study drug, will be used for the derivation of baseline value.

Change from Baseline: Assessment value at post-dosing visit – baseline value. It should be noted that if the derived baseline as above is missing for one parameter, then the change from baseline will not be available for this parameter. Imputation of baseline data will not be conducted.

Percentage Change from Baseline:
(Assessment value at post-dosing visit – baseline value)*100 / baseline value

11. EFFICACY

11.1. Primary and Secondary Efficacy Analysis: UNC DEMS Reduction

UNC DEMS is used to measure the primary and one of the secondary endpoints. UNC DEMS score is rated from 1 to 10, with a higher score associated more severe dry eye symptoms. Data are NOT collected separately for study/fellow eyes. UNC DEMS is assessed at each study visit.

The primary endpoint is the proportion of subjects with clinically significant improvement from baseline in UNC DEMS score at Visit 3 (Day 8). A clinically significant improvement is defined as a minimum reduction in UNC DEMS score of 1 unit or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures.

One of the secondary endpoints is the proportion of subjects with clinically significant improvement from baseline in UNC DEMS score at Visit 4 (Day 15). A clinically significant improvement is defined as a minimum reduction in UNC DEMS score of 1 unit or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 4 (Day 15) will be treated as failures.

Responder Analysis

Subjects with 1 unit or more reduction in UNC DEMS score from baseline are defined as responders, and response rates will be summarized at Visit 3 (Day 8) and Visit 4 (Day 15). All other subjects with non-missing data will be treated as non-responders. Further, subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8)/Visit 4 (Day 15) will be treated as failures. It should be noted that subjects will be treated as non-responders from the time point that they received non-study treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy.

For the ITT responder analysis, the analysis will be conducted based on the observed available

data without any imputation for missing data.

The responder rate will be summarized at Visit 3 (Day 8) and Visit 4 (Day 15) by treatment group, along with its 95% CI which will be estimated by Clopper-Pearson exact method. The difference in responder rates between each of the SURF- 200 formulations and vehicle at each visit will be compared by Fisher's exact method.

11.2. Secondary Endpoint: Conjunctival Hyperemia Grade Reduction

Conjunctival hyperemia grade is used to measure one of the secondary endpoints, and will be assessed using a consistent light source, examiner and exam room from visit to visit. Conjunctival hyperemia is graded from 0 to 3, with a higher grade (score) associated more severe conditions. Data are collected separately for study/fellow eyes. Conjunctival hyperemia is assessed at each study visit.

The proportion of subjects with clinically significant improvement from baseline in conjunctival hyperemia in the study eyes at Visit 3 (Day 8) will be summarized for each treatment group. A clinically significant improvement is defined as a reduction of 0.5 points or more. Subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures.

Responder Analysis

Subjects with 0.5 point or more reduction in conjunctival hyperemia grade (score) from baseline are defined as responders, and responder rates will be summarized at Visit 3 (Day 8). All other subjects with non-missing data will be treated as non-responders. Further, subjects who receive another therapeutic treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy at or prior to Visit 3 (Day 8) will be treated as failures. It should be noted that subjects will be treated as non-responders from the time point once they received non-study treatment for the signs and symptoms of their episodic flare up due to a lack of efficacy.

For the ITT responder analysis, the first analysis will be conducted based on the observed available data without any imputation for missing data.

The same responder analysis as conducted for the primary endpoint will be conducted for conjunctival hyperemia response analysis. That is, for each treatment group, the responder rates and their Clopper-Pearson exact 95% CIs will be estimated at Visit 3 (Day 8). The responder rate difference and its 95% CI between each of the SURF-200 formulations (0.02% and 0.04% BSP) vs vehicle at Visit 3 (Day 8) will be estimated as well. The difference in responder rates between each of the SURF-200 formulations and vehicle at each visit will be compared by Fisher's exact method.

The responder analysis for conjunctival hyperemia grade is only applicable to study eye data.

12. SAFETY

12.1. Adverse Events

Adverse events will be summarized separately for those occurring in the study eye, in the fellow eye, and non-ocular events. For overall AE incidence summary, one table for ocular AEs (study eye and fellow eye combined) will be reported. In this table, each subject will be counted only once in each summary category, to avoid correlated data. However, the results should be interpreted with caution because fellow eyes are selective samples by study design. Regardless of whether the fellow eye is treated or not, all AEs reported for the fellow eye will be included for the safety analysis. AEs marked as 'Both Eyes (OU)' from the AE CRF page will be summarized both for study eye and fellow eye.

All AE verbatim terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 Update. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred term (PT) will be of primary interest for the analysis.

Treatment emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened on or after the date of first administration of study drug. If missing dates or time prevent a clear determination as to whether the AE is treatment emergent, the AE will be regarded as a TEAE.

While all AEs will be summarized, the main AE summaries will be restricted to TEAEs only. Treatment emergent adverse events will be summarized descriptively. For the summary of TEAEs, if a subject experienced the same AE multiple times, this will only be counted once for the purpose of counting the number of patients experiencing that AE. Summary tables will include the number of subjects (%) experiencing an AE and the number of AEs.

The TEAE summaries will include:

- Overall Summary of Subjects with at Least One Adverse Event
- Summary of TEAEs by SOC and PT
- Summary of TEAEs with an Incidence >=5% by SOC and PT
- Summary of Serious TEAEs by SOC and PT