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Phase 2 Clinical Study Protocol, Amendment 01 including Statistical Analysis Plan

A Multicenter, Randomized, Double-masked Study to Evaluate the Safety, Tolerability, and Efficacy of SURF-100 Ophthalmic Solution (a Mycophenolic Acid/Betamethasone Sodium Phosphate Combination) in Subjects with Dry Eye Disease

Original Protocol:	29 April 2020
Protocol Amendment 01:	28 August 2020
Statistical Analysis Plan:	05 December 2021

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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
DED	dry eye disease
eCRF	electronic case report form
e.g.	exempli gratia; for example
etc.	et cetera
ETDRS	early treatment diabetic retinopathy study
°F	degrees Fahrenheit
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
i.e.	id est; in other words
IOP	intraocular pressure
IRB	institutional review board
ITT	intent to treat
IV	intravenous
LASIK	laser-assisted in situ keratomileusis
LOCF	last observation carried forward
logMAR	log of the minimum angle of resolution
MedDRA®	Medical Dictionary for Regulatory Activities
mg/kg/per day	milligram per kilogram per day
mm	millimeter
MMF	mycophenolate mofetil
mmHg	millimeters of mercury
MPA	mycophenolic acid
No.	Number
NSAID	nonsteroidal anti-inflammatory drug
PP	per protocol
PRN	pro re nata; as needed
PT	preferred term
SAE	serious adverse event
SD	standard deviation

Abbreviation or Acronym	Definition
SOC	system organ class
SOP	standard operating procedure
SURF-100	mycophenolic acid 0.3% and betamethasone sodium phosphate 0.01%
TBUT	tear break-up time
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
UNC DEMS	University of North Carolina Dry Eye Management Scale
VA	visual acuity

1. STUDY OBJECTIVE

To evaluate the ocular safety, tolerability, and efficacy of the topical administration of SURF-100 ophthalmic solution, a combination of 0.3% mycophenolic acid (MPA) and 0.01% betamethasone sodium phosphate (BSP), compared to:

- 0.1% MPA
- 0.3% MPA
- 0.01% BSP
- Vehicle
- 0.05% cyclosporine ophthalmic emulsion
- 5% lifitegrast ophthalmic solution

2. STUDY DESIGN

This study is a Phase 2, multicenter, randomized, double-masked, parallel-group clinical trial in subjects with dry eye disease (DED). Subjects 18 years of age and older with a diagnosis of dry eye disease 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.

During the screening period (Day -14 to Day 0) of the study, subject eligibility will be determined. All eligibility criteria must be met for randomization into the study. Subjects who meet all inclusion and none of the exclusion criteria at the Screening Visit may proceed directly to Visit 2 on Day 0 for randomization. Subjects who fail screening may be re-screened once and should repeat Screening Visit 1 (Day -14 to Day 0) within 30 days of the original screening visit. Approximately 280-350 subjects at approximately 40 investigational sites located in the United States who meet all study entry criteria will be randomized at Visit 2 (Day 0) in a balanced ratio to 1 of 7 treatment groups:

- SURF-100 (0.3% MPA/0.01% BSP)
- 0.1% MPA
- 0.3% MPA
- 0.01% BSP
- Vehicle
- 0.05% cyclosporine ophthalmic emulsion
- 5% lifitegrast ophthalmic solution

The study eye will be determined by the investigator based on the results of the ophthalmic examination. Some subjects may have both eyes qualify for the study. In these cases, data from the eye with the worst combined clinical signs and symptoms score at Visit 2 (Day 0), or at Visit 1 (Day -14 to Day 0) if Visit 2 is <5 days after Visit 1, will be identified as the study eye and will be analyzed for safety and efficacy throughout the study. If the total score is the same for both

eyes, the right eye will be designated as the study eye and data from the right eye will be analyzed for safety and efficacy.

Subjects will be randomly assigned to receive treatment twice daily (BID) for 84 days (Days 0 to 83). Subjects will receive instructions for dosing at home and for completing a dosing diary during the study dosing period (Visit 2 [Day 0] to Visit 6 [Day 84]).

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 one dose BID (preferably 8-12 hours apart) in the study eye on Days 0 to 83.

If deemed necessary by the investigator, study drug may also be instilled in the fellow eye. If the investigator deems that the fellow eye should also be treated, then the same unit-dose container used to dose the study eye should be used to deliver a dose to the fellow eye. If both eyes are treated with study drug, all study assessments will be performed on the treated eyes, but the fellow eye will only be analyzed for safety while the study eye will be analyzed for safety and efficacy.

During the dosing phase (Day 0 to Day 83), subjects will self-instill (or will have study drug instilled by the subject's caregiver) one drop of study drug BID on the study eye for 84 days. Subjects will then be followed for approximately 2 weeks during the evaluation phase (Day 84 to Day 98).

There will be 7 study visits for full study participation: 1 visit during the screening phase, 4 visits (Day 0, Day 7, Day 30, and Day 60) during the dosing phase, and 2 visits (Day 84 and Day 98) during the post-treatment evaluation phase.

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:

Primary efficacy endpoint: University of North Carolina Dry Eye Management Scale (UNC DEMS)
A reduction of 10% in patient-reported DED symptoms and reduction of impact of symptoms on daily life at Day 84 as defined by the UNC DEMS with SURF-100 as compared to vehicle, 0.05% cyclosporine ophthalmic emulsion, and 5% lifitegrast ophthalmic solution.

Secondary efficacy endpoints:

1. **Tear Break-up Time (TBUT)**
   Average increase in TBUT at Day 84 for SURF-100 compared to vehicle, 0.05% cyclosporine ophthalmic emulsion, and 5% lifitegrast ophthalmic solution.
2. **Schirmer Tear Test**
   Average increase in Schirmer score test (with anesthesia) at Day 84 for SURF-100 compared to vehicle, 0.05% cyclosporine ophthalmic emulsion, and 5% lifitegrast ophthalmic solution.

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

Adult subjects (≥18 years) diagnosed with DED will be considered for study entry. DED is defined as a minimum score of greater than or equal to 5 but less than or equal to 9, as assessed by the UNC DEMS questionnaire, TBUT equal to or less than 5 seconds and Schirmer tear test (with anesthesia) of equal to or less than 10 millimeters (mm), but more than 1 mm.

4.1. Inclusion Criteria

The following are inclusion criteria for prospective study subjects to be confirmed at Visit 1 (Day -14 to Day 0) prior to randomization.

1. Adults at least 18 years of age at the time of the Screening visit.

2. Willing and able to read, sign, and date the informed consent form (ICF) after the nature of the study has been explained and any questions have been answered, and prior to initiation of any study procedures or exams.

3. Willing and able to comply with all study procedures and attend all study visits.

4. Willing to suspend use of tear substitutes at least 72 hours prior to Visit 2 (Day 0) through Visit 7 (Day 98).

5. Best corrected visual acuity (BCVA) of 0.7 log of the minimum angle of resolution (logMAR) or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1 (Day -14 to Day 0).

6. Subject-reported history of dry eye in both eyes.

7. Meeting ALL of the following criteria in the same eye at Visit 1 (Day -14 to Day 0) and meeting ALL of the following criteria in the same eye at Visit 2 (Day 0) if Visit 2 is performed >5 days after Visit 1:
   a) Minimum score of greater than or equal to 5 but less than or equal to 9 on UNC DEMS questionnaire.
   b) Schirmer Tear Test (with anesthesia) equal to or less than 10 mm, but more than 1 mm
   c) TBUT: Equal to or less than 5 seconds

8. A negative urine pregnancy test if female and of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses] or premenarchal) and must have used adequate birth control throughout the study period (through Visit 7 [Day 98]). Adequate birth control is defined as hormonal-oral, implantable, injectable, or transdermal contraceptives; mechanical - spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; abstinence; or surgical sterilization of male partner.

9. Subjects with secondary Sjögren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosus) or other autoimmune diseases (e.g., multiple sclerosis, inflammatory bowel disease) are eligible for study consideration provided the subject meets all other inclusion and exclusion criteria, AND are not in a medical state - in the opinion of the principal investigator - that could interfere with study parameters, are not taking systemic/ocular steroids, and are not immunodeficient/ immunosuppressed (e.g., receiving systemic immunomodulating or immunosuppressive drugs to manage their baseline medical state).

4.2. Exclusion Criteria

The following are exclusion criteria for prospective study subjects to be confirmed from Day -14 – Day 0 (at Visit 1) prior to randomization:

1. Contraindications or known hypersensitivity to the study drug(s), including RESTASIS or XIIDRA, or their components.

2. Subjects who are employees or immediate family members of employees at the investigational site.

3. Subjects who are members of the same household.

4. Any ocular condition that, in the opinion of the investigator, may affect study parameters including, but not limited to, lid margin disorders (e.g., blepharitis including staphylococcal, demodex, or seborrheic; excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann’s nodular degeneration, and asthenopia-related conditions, allergic conjunctivitis, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, and/or active ocular inflammation.

5. Any condition that could affect trigeminal nerve function including facial or ocular Herpes Zoster/Shingle, a stroke or nerve palsy affecting the eye(s).

6. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease in either eye within 14 days prior to Visit 2 (Day 0).

7. Active or history of ocular herpes or any other ocular infection in either eye within the last 30 days prior to Visit 1 (Day -14 to Day 0).

8. Unwilling to avoid wearing contact lenses for 7 days prior to Randomization (Visit 2, Day 0) and for the duration of the study period (through Visit 7, Day 98).

9. Positive urine pregnancy test at Screening, nursing an infant or planning to become pregnant during the study.

10. Any blood donation or significant loss of blood within 56 days of Visit 1 (Day -14 to Day 0).

11. Any history of immunodeficiency disorder, human immunodeficiency virus (HIV), positive hepatitis B, C, or evidence of acute active hepatitis A (anti-hepatitis A virus immunoglobulin M), or organ or bone marrow transplant.

12. Any medication (oral or topical) known to cause ocular drying that is not administered as a stable dose for at least 30 days prior to Visit 1 (Day -14 to Day 0) and for the duration of the study (Visit 7, Day 98); antihistamines are not allowed at any time during the study.

13. Use of prohibited medications (topical, topical ophthalmic and/or systemic, during the appropriate pre-study washout period (see below) and during the study. Prohibited medications include topical cyclosporine or lifitegrast, use of any other ophthalmic medication (e.g., glaucoma medication, topical anti-inflammatory eye drops) for the duration of the study (refer to the full list of Disallowed Medications in Concomitant Medications, Section 7, for more information regarding prohibited medications during the study).

    NOTE: Supplements containing omega-3 are allowed if the subject has been taking said supplement for at least 3 months prior to Screening. Subjects are not allowed to begin taking supplements containing omega-3 during the study. The appropriate pre-study washout period is as follows:
    a) Antihistamines (including ocular): 7 days prior to Visit 1 (Day -14 to Day 0).
    b) Topical cyclosporine or lifitegrast or omega-3s within 14 days prior to Visit 1 (Day -14 to Day 0).
    c) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1 (Day -14 to Day 0).
    d) Depot-corticosteroids in either eye at least 45 days prior to the first dose of study drug (Day 0)
    e) All other topical ophthalmic preparations (including artificial tear substitutes other than the study drops): 72 hours prior to Visit 1 (Day -14 to Day 0).
    f) Introduction of any new, nonsteroidal anti-inflammatory drugs (NSAIDs) including but not limited to topical, systemic (including sleep-aids containing NSAIDs), inhaled, or irrigation solution within 7 days prior to the first dose of study drug. Subjects who are on

stable dose of NSAIDs (stable for at least 4 weeks prior to the first dose of study drug) are eligible for participation and should remain on a stable dose throughout the duration of the study (i.e., through Day 98).

g) Triamcinolone in either eye at least 90 days prior to the first dose of study drug (Day 0).
h) 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 (Day 0).
i) Systemic pain relievers, analgesics (e.g., pregabalin, gabapentin, opioids) 14 days prior to the first dose of study drug (Day 0).
j) Any supplement, prescribed medication or over-the-counter product that the investigator feels may interfere with the study parameters, including homeopathic remedies, analgesics, and pain medication.
k) Oral doxycycline within 6 months of first dose of study drug (Day 0).
l) Diuretics: Within 28 days prior to Visit 1 (Day -14 to Day -1).
m) Punctal occlusion:
    i. Punctal cauterization: Randomization may not occur until 4 weeks following the procedure.
    ii. Permanent/semi-permanent punctal plugs (this includes 180-day punctal plugs): Randomization may not occur until 4 weeks following the procedure. If a punctal plug falls out during the study, it should be reinserted.
    iii. Temporary collagen punctal plugs: Not permitted. If subject has a history of use of temporary punctal plugs, randomization may not occur until 4 weeks since last insertion and puncta are plug-free, as determined by the investigator.

14. Any significant chronic illness that, in the opinion of the investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes.

15. Use of any investigational product or device within 30 days prior to Visit 1 (Day -14 to Day 0) or during the study period.

16. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1 (Day -14 to Day 0), and/or any other ocular surgical procedure within 12 months prior to Visit 1 (Day -14 to Day 0); or any scheduled ocular surgical procedure during the study period.

17. Use of any laser procedure for the eyes in the 30 days prior to Visit 1 (Day -14 to Day 0).

18. Known history of alcohol and/or drug abuse within the past 12 months that in the opinion of the principal investigator, may interfere with study compliance, outcome measures including safety parameters, and/or the general medical condition of the subject.

19. Subjects with dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens Johnson syndrome, cicatricial pemphigoid) or destruction of conjunctival goblet cells (as with vitamin A deficiency) are not eligible for the study. Subjects with incidental scars secondary to refractory surgery (i.e., LASIK surgery) that, in the opinion of the principal investigator, would not interfere with study compliance and/or outcome measures, are not excluded from the study.

20. Subjects who test positive for the COVID-19 virus within 30 days prior to Visit 1 (Day -14 to Day 0).

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 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 assigned unique randomization number, will also be present on the label.

One study drug kit will be provided to the subject on Visit 2 (Day 0), Visit 4 (Day 30) and Visit 5 (Day 60). Each study drug kit will be provided as a labeled, tamper-sealed carton containing one labeled plastic disposal bag and 13 sealed, labeled foil laminate pouches. Each foil laminate pouch will contain one band of 5 single unit-dose containers.

Each study drug kit will also have a tear-off label portion that includes the labeling information described above. This tear-off label will be placed in the subject's source record at the time each study drug kit is dispensed to the subject.

As the study drug is sterile and provided as single unit-dose containers, subjects (or their caregivers) will be required to use a new container for the morning dose and a new container for the evening dose. During the 84-day dosing period, a total of 168 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 by the subject (or their caregiver), or in both eyes if deemed necessary by the investigator. However, the 3 study drug kits assigned to a subject will contain enough single unit-dose containers for a total of 195 doses (27 additional single unit-dose containers are provided in the event of a mishap, missed study visit, etc.). Therefore, subjects (or their caregivers) will be cautioned to dose only for the specified amount of time and specified number of doses.

6. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindications:

SURF-100 or any of the comparative treatment arms containing MPA should not be used in patients with hypersensitivity to mycophenolate sodium, MPA or mycophenolate mofetil (MMF) or to any of the excipients.

Betamethasone sodium phosphate, 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.

Cyclosporine ophthalmic emulsion 0.05% is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation (refer to Cyclosporine Ophthalmic Emulsion 0.05% Prescribing Information).

Lifitegrast ophthalmic solution 5% is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation (refer to Lifitegrast Ophthalmic Solution 5% Prescribing Information).

Warnings and Precautions:

Betamethasone sodium phosphate (BSP)	Ocular adverse reactions which may occur with SURF-100 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.
Mycophenolic acid (MPA)	Systemic exposure associated with ophthalmic application of MPA has not been evaluated in humans. Adverse reactions from topical ophthalmic administration of MPA have not been established or investigated to date.
Cyclosporine ophthalmic emulsion 0.05%	To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces. Cyclosporine ophthalmic emulsion 0.05% should not be administered while wearing contact lenses. (Refer to the Cyclosporine Ophthalmic Emulsion 0.05% Prescribing Information).
Lifitegrast ophthalmic solution 5%	No warnings/precautions are listed in the Lifitegrast Ophthalmic Solution Prescribing Information. (Refer to the Lifitegrast Ophthalmic Solution 5% Prescribing Information).

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:

Undesirable effects for the components of BSP, MPA, and the commercial reference therapies cyclosporine ophthalmic emulsion 0.05% and lifitegrast ophthalmic solution 5% are listed below.

Betamethasone sodium phosphate (BSP)	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
Mycophenolic acid (MPA)	Systemic exposure associated with ophthalmic application of MPA has not been evaluated in humans. Adverse reactions from topical ophthalmic administration of MPA have not been established or investigated to date.
Cyclosporine ophthalmic emulsion 0.05%	In clinical trials the most common adverse reaction following the use of cyclosporine ophthalmic emulsion 0.05% was ocular burning (17%). Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring). Refer to the Cyclosporine Ophthalmic Emulsion 0.05% Prescribing Information for a summary of post-approval adverse reactions reported for cyclosporine ophthalmic emulsion 0.05%.
Lifitegrast ophthalmic solution 5%	The most common adverse reactions (incidence 5-25%) following the use of lifitegrast ophthalmic solution 5% were instillation site irritation, dysgeusia and decreased visual acuity. Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis. Refer to the Lifitegrast Ophthalmic Solution 5% Prescribing Information for a summary of post-approval adverse reactions reported for lifitegrast ophthalmic solution 5%.

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 any of the randomized treatments is unlikely to lead to any serious adverse effects.

Drug-Drug Interactions:

No topical ophthalmic drug-drug interactions are known for the randomized treatments.

Effects on Ability to Drive and Use Machines:

Randomized treatments 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.

Pregnancy:

Study treatments should not be administered to pregnant or lactating women, as their safety for use during pregnancy and lactation has not been established.

The effect on fertility has not been established for SURF-100. No reproductive toxicity or fertility studies have been conducted with SURF-100.

There are no adequate and well-controlled studies of cyclosporine ophthalmic emulsion 0.05% in pregnant women. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose (refer to the Cyclosporine Ophthalmic Emulsion 0.05% Prescribing Information).

There are no available data on lifitegrast ophthalmic solution 5% use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures (refer to the Lifitegrast Ophthalmic Solution 5% Prescribing Information).

7. CONCOMITANT MEDICATIONS

Disallowed medications include:

- Antihistamines (including sleep-aids containing an antihistamine) at least 7 days prior to Visit 1 (Day -14 to Day 0) and through Day 98.
- Topical cyclosporine or lifitegrast or omega-3s within 14 days prior to Visit 1 (Day -14 to Day 0) and through Day 84. Supplements containing omega-3 are allowed if the subject has been taking said supplement for at least 3 months prior to Screening. Subjects are not allowed to begin taking supplements containing omega-3 during the study.
- Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1 (Day -14 to Day 0) and through Day 84.
- Depot-corticosteroids in either eye at least 45 days prior to the first dose of study drug (Day 0) and through Day 84.
- All other topical ophthalmic preparations (including artificial tear substitutes) at least 72 hours prior to Visit 2 (Day 0) through Visit 7 (Day 98).
- Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease in either eye within 14 days prior to Visit 2 (Day 0) through Visit 7 (Day 98).

- Introduction of any new, nonsteroidal anti-inflammatory drugs (NSAIDs) including but not limited to topical, systemic (including sleep-aids containing NSAIDs), inhaled, or irrigation solution within 7 days prior to the first dose of study drug is not permitted. Subjects who are on stable dose of NSAIDs (stable for at least 4 weeks prior to the first dose of study drug) are eligible for participation and should remain on a stable dose throughout the duration of the study (i.e., through Day 98). If a subject takes an NSAID as needed (PRN) during the conduct of the study, that is permitted but subjects should be requested not to take an NSAID within the 24 hours prior to a scheduled study visit.
- Triamcinolone in either eye at least 90 days prior to the first dose of study drug (Day 0) and through Day 84.
- 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 (Day 0) through Day 84.
- Systemic pain relievers, analgesics (e.g., pregabalin, gabapentin, opioids) 14 days prior to the first dose of study drug (Day 0) through Day 98.
- Any supplement, prescribed medication or over-the-counter product that the investigator feels may interfere with the study parameters, including homeopathic remedies, analgesics, and pain medication through Day 84.
- Oral doxycycline within 6 months of first dose of study drug (Day 0) through Day 84.
- Diuretics: Within 28 days prior to Visit 1 (Day -14 to Day -1) through Day 84.

Prior medications (both prescription and non-prescription [including over the counter medicine, vitamins, supplements, and herbal supplements]) taken within 3 months before the screening visit will be recorded in the source documents and entered on the appropriate electronic case report form (eCRF). 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

Subject Completed Assessments:

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 0) if Visit 2 is >5 days following Visit 1. The UNC DEMS will also be completed by subjects at Visit 3 (Day 7) through Visit 7 (Day 98).

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 every 7 days during the dosing period (Day 0 to Day 83).

Investigator Assessments:

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 0) [prior to randomization] in both eyes if Visit 2 is >5 days following Visit 1. BCVA will also be performed in treated eyes at Visit 3 (Day 7) through Visit 7 (Day 98). 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 0) [prior to randomization] if Visit 2 is >5 days following Visit 1. Slit lamp biomicroscopy will also be performed in treated eyes at Visit 3 (Day 7) through Visit 7 (Day 98).

Ophthalmoscopy: An undilated ophthalmoscopy exam will be performed in both eyes at Visit 1 (Screening; Day -14 to Day 0) and in treated eyes at Visit 7 (Day 98).

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 0) [prior to randomization] if Visit 2 is >5 days following Visit 1. IOP will also be measured in treated eyes at Visit 3 (Day 7) through Visit 7 (Day 98).

Conjunctival Hyperemia Assessment: Conjunctival hyperemia will be assessed in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 0) [prior to randomization] if Visit 2 is >5 days following Visit 1. Conjunctival hyperemia will also be assessed in the treated eye(s) at Visit 3 (Day 7) through Visit 7 (Day 98).

Tear Break-up Time (TBUT): TBUT will be conducted in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 0) [prior to randomization] if Visit 2 is >5 days following Visit 1. TBUT will also be measured in the treated eye(s) at Visit 3 (Day 7) through Visit 7 (Day 98).

Fluorescein Corneal Staining: Fluorescein corneal staining will be conducted in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 0) if Visit 2 is >5 days following Visit 1. Fluorescein corneal staining will also be measured in the treated eye(s) at Visit 3 (Day 7) through Visit 7 (Day 98).

Conjunctival Staining: Conjunctival staining using fluorescein dye will be conducted in both eyes at Visit 1 (Screening; Day -14 to Day 0) and only at Visit 2 (Day 0) if Visit 2 is >5 days following Visit 1. Conjunctival staining will also be measured in the treated eye(s) at Visit 3 (Day 7) through Visit 7 (Day 98).

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 0) if Visit 2 is >5 days following Visit 1. Schirmer tear tests (with anesthesia) will also be conducted in the treated eye(s) at Visit 3 (Day 7) through Visit 7 (Day 98) 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 6 (Day 0 through Day 84), 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 treatment groups in a balanced 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 schedule is generated by an un-masked statistician who is not affiliated with the study. The randomization schedule 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(s): The primary endpoint is a reduction of ≥10% in patient-reported DED symptoms and impact of symptoms on daily life at Day 84 as defined by the UNC DEMS with SURF-100 as compared to 5% lifitegrast ophthalmic solution, 0.05% cyclosporine ophthalmic emulsion, and vehicle. Subjects not responding to study treatment (non-responders) and who receive another therapeutic treatment for the signs and symptoms of dry eye at or prior to Visit 6 (Day 84) will be treated as failures.

Secondary Efficacy Endpoints:

- Tear Break-up Time: Average increase in TBUT at Day 84 for SURF-100 compared to 5% lifitegrast ophthalmic solution, 0.05% cyclosporine ophthalmic emulsion, and vehicle.
- Schirmer tear test: Average increase in Schirmer tear test score (with anesthesia) at Day 84 for SURF-100 compared to 5% lifitegrast ophthalmic solution, 0.05% cyclosporine ophthalmic emulsion, and vehicle.

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

10.3. Analysis Populations

Safety Population: The safety population includes all randomized 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.

Intent-to-Treat Population: The Intent-to-Treat (ITT) population includes all randomized subjects. 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 in the ITT population who have no significant protocol deviations during the study.

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. As per the protocol, an ITT analysis with the last-observation-carried-forward (LOCF) method will be conducted for the primary efficacy analysis.

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.
- 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.
- 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.

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. In the protocol, the first dosing day is denoted as Day 0, which is corresponding to Study Day 1. 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 eCRF 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 Efficacy Analysis

Subjects with a 10% or more reduction in UNC DEMS score from baseline are defined as responders, and response rates at Visit 6 (Day 84) will be summarized by treatment group. All other subjects with non-missing data will be treated as non-responders. Further, subjects who received non- study therapeutic treatment for the signs and symptoms of dry eye at or prior to Visit 6 (Day 84) will be treated as non-responders (treatment failure) from the time of receiving non-study therapeutic treatment regardless of whether the UNC DEMS score is available at the relevant visit. For the ITT analysis, subjects with a missing UNC DEMS score at a visit will be imputed by the LOCF method. Therefore, there will be no missing data for ITT analysis. The response rate will be summarized at Visit 6 (Day 84) by treatment group, along with its 95% CI which will be estimated by Clopper-Pearson exact method. The response rate difference between SURF-100 and each of the comparison treatment groups will be reported as well, with 95% CI of the difference estimated by the method of Newcombe with continuity correction. The difference in response rate between SURF-100 and other comparison treatment groups will be compared by Fisher's exact method.

11.2. Secondary Efficacy Analyses

Secondary Endpoint: Based on TBUT at Day 84:

Tear Break-Up Time will be assessed 3 times at each study visit for each subject. The mean of the 3 measurements will be used as the source data for the analysis.

Mixed Model for Repeated Measures (MMRM): The absolute change from baseline in TBUT at Day 84 is the one of the pre-specified secondary endpoints, and the treatment effect based on the absolute change from baseline in TBUT at Day 84 will be the focus of interest. The MMRM will include fixed effects of baseline TBUT, age, treatment, visit, and treatment by visit interaction. The least squares means of the absolute change from baseline in TBUT and their 95% CIs at Day 84 will be estimated from the MMRM model for each treatment group. The treatment effect, the difference of least squares means between SURF- 100 and each of the comparison treatment groups, and its 95% CI and p-value comparing the treatment effect at each visit will be estimated from the model as well. This analysis is only applicable to study eye.

Secondary Endpoint: Based on Schirmer Tear Test (with Anesthesia) at Day 84:

Mixed Model for Repeated Measures (MMRM): The absolute change from baseline in Schirmer tear test score at Day 84 is one of the pre-specified secondary endpoints, and the treatment effect based on the absolute change from baseline in Schirmer tear test score at Day 84 will be the focus of interest. The MMRM will include fixed effects of baseline Schirmer tear test score, age, treatment, visit, and treatment by visit interaction. The least squares means of the absolute change from baseline in Schirmer tear test score and their 95% CIs at Day 84 will be estimated from the MMRM model for each treatment group. The treatment effect, the difference of least squares means between SURF-100 and each of the comparison treatment groups, and its 95% CI and p-value comparing the treatment effect at each visit will be estimated from the model as well. This analysis is only applicable to the study eye.

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