NCT04324359

Sponsor: Surface Ophthalmics Inc.

09 October 2020

Study Number C-201-001
Phase 2 Clinical Study Protocol, Amendment 02 including Statistical Analysis Plan

A Multicenter, Randomized, Double-masked Study To Compare the Ocular Safety, Tolerability, and Efficacy of SURF-201 Ophthalmic Solution (0.2% Betamethasone Sodium Phosphate) to Vehicle in Cataract Surgery Subjects

Original Protocol:	30Sep2019
Protocol Amendment 01 Date:	15Jan2020
Protocol Amendment 02 Date:	09 Oct 2020

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LIST OF ABBREVIATIONS

Abbreviation or Acronym	Definition
ACC	anterior chamber cell
AE	adverse event
BCVA	best-corrected visual acuity
BID	twice daily
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
etc.	et cetera
ETDRS	early treatment diabetic retinopathy study
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
i.e.	id est; in other words
IOL	intraocular lens
IOP	intraocular pressure
IRB	institutional review board
ITT	intent to treat
IUD	intrauterine device
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
mm	millimeter
mmHg	millimeters of mercury
NDA	new drug application
No.	number
NSAID	nonsteroidal anti-inflammatory drug
PP	per protocol
PT	preferred term
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
TLF	tables, listings, and figures
VA	visual acuity
VAS	visual analog scale

1. STUDY OBJECTIVE

To evaluate the ocular safety, tolerability, and efficacy of topical administration of SURF-201 (0.2% betamethasone sodium phosphate [BSP] ophthalmic solution) compared with vehicle when dosed twice daily (BID) for 1 day prior to cataract surgery, the day of cataract surgery, and 14 days post cataract surgery.

2. STUDY DESIGN

This study is a Phase 2, multicenter, randomized, double-masked, vehicle-controlled, parallel-group clinical trial. 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 phase (Day -2 to Day -14) of the study, subjects who meet all inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio: 40 subjects in the 0.2% BSP group and 40 subjects in the vehicle group.

During the dosing phase (Day -1 to Day 14), subjects will dose BID for 16 days: the day before cataract surgery, the day of cataract surgery, and for 14 days after cataract surgery. Subjects will then be followed for approximately 2 weeks during the evaluation phase (Day 15 to Day 32).

There will be 7 study visits for full study participation: 1 visit during the screening phase, 3 visits (Day 0, Day 1 and Day 8) during the dosing phase, and 3 visits (Day 15, Day 22, and Day 32) during the evaluation phase.

Subjects will instill 3 doses of study drug prior to surgery (2 doses on Day -1, and 1 dose on Day 0 prior to surgery), 1 dose in the evening after surgery and continue dosing BID for 14 days after surgery.

Subject safety will be evaluated throughout the study. The safety parameters to be assessed are the incidence 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.

Efficacy will be assessed by biomicroscopic measurement of anterior chamber cells (ACCs) and measurement of the subject's pain level at each visit using a visual analog scale (VAS). Subject pain will also be assessed by subjects at home using a subject diary.

All 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

Approximately 80 subjects, 18 years of age and older, who are scheduled to undergo uncomplicated unilateral cataract surgery (phacoemulsification or extracapsular extraction; surgery must not be performed with the aid of a femto [femtosecond] laser) and who meet all study entry criteria will participate in the study.

4.1.Inclusion Criteria

The following are inclusion criteria for prospective study subjects to be confirmed at Visit 1 (Day -14 – Day -2) prior to randomization.

1. Adult subjects, age 18 years or older, scheduled for uncomplicated unilateral cataract surgery (phacoemulsification or extracapsular extraction; surgery must not be performed with the aid of a femto [femtosecond] laser) with posterior chamber intraocular lens implantation.

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 intraocular pressure (IOP) of >8 mmHg and ≤22 mmHg in the study eye (surgery eye).

6. Subject must agree to maintain their current dosing regimen throughout the study period (from Screening through Day 32) if they are currently using topical cyclosporin-A or Xiidra (lifitegrast 5%).

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

8. 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).

9. Subjects must agree to avoid any medications which are disallowed (as defined by the protocol).

4.2. Exclusion Criteria

The following are exclusion criteria for prospective study subjects to be confirmed from Day -14 – Day -2 (at Visit 1) prior to randomization:

1. Subject has any intraocular inflammation (cells and flare in the anterior chamber) or ocular pain (pain score of >0) in either eye prior to surgery.

2. Subject has any extraocular inflammation in the study eye prior to surgery (blepharitis is allowed if only scurf is present without any concurrent conjunctivitis or lid erythema/edema) or ongoing uveitis.

3. Subject has a history of diabetic retinopathy and/or previous vitrectomy in the study eye within the last 2 years prior to Screening which, in the investigator's opinion, is clinically significant and could impact the normal outcome of an uncomplicated cataract surgery.

4. Subject has a diagnosis of severe dry eye in the study eye.

5. Subject has any sign of iritis or scleritis in the study eye.

6. Subject has a history of glaucoma surgery in the study eye within the last 2 years prior to Screening.

7. Subject has a history of retinal surgery in the study eye within the last 2 years or plans to undergo retinal surgery in the study eye during the study period (from Screening through Day 32)

8. Subject has a history of Fuchs' dystrophy in the study eye.

9. Subject has guttata or chalazion in the study eye.

10. Subject has undergone radial keratotomy, photorefractive keratotomy, advanced surface ablation, corneal transplant, or LASIK in the study eye within the last 2 years prior to Screening.

11. Subject plans to undergo cataract surgery in the non-study (fellow) eye during the study period (from Screening through Day 32).

12. Subject plans to undergo additional ocular surgery (including femtosecond laser-assisted cataract surgery, minimally invasive glaucoma surgery, astigmatic keratotomy, limbal relaxing incision surgery, mechanical pupillary expanders, conjunctival incisions, and vitrectomy) in either eye during the study period (from Screening through Day 32).

13. Subject has a history of intraocular injections in the study eye within 6 months prior to Screening.

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

15. Subject has active corneal, conjunctival or canalicular pathology (including ocular infection [bacterial, viral or fungal]) in the study eye. Specifically, 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 the ocular structures (such as fungal keratitis).

16. Subject has thinning of the cornea or sclera.

17. Subject plans to undergo uncomplicated unilateral cataract surgery with the aid of anterior capsular staining products (e.g., Trypan blue) or with the aid of a femto (femtosecond) laser.

18. Subject has undergone anti-neoplastic therapy within the last 2 years prior to Screening or plans to undergo anti-neoplastic therapy during the study period.

19. Subject has a history of use of medications to treat benign prostatic hyperplasia that, in the opinion of the investigator, limits adequate dilation of the pupil to safely perform uncomplicated cataract removal and IOL implantation.

20. Subject has a history of liver disease within the last 5 years prior to Screening.

21. Subject has a history of previous ocular trauma in the study eye that places the study eye at risk of increased post-surgical complications or inflammation.

22. Subject has or had a known blood dyscrasia or bone marrow suppression.

23. Subject has an active or chronic/recurrent ocular or systemic disease that is not controlled and may have an impact on would healing (e.g., diabetes mellitus, systemic connective tissue disease, severe atopic disease).

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

25. Subject has a known hypersensitivity or poor tolerance to betamethasone and/or betamethasone sodium phosphate or any component of the study drug or any of the procedural medications such as anesthetic and/or fluorescein drops, dilating drops, etc.

26. Female subjects who are currently pregnant or nursing or are planning to become pregnant during the study or have a positive pregnancy test.

27. Subject has previously participated in this study protocol.

28. Subject used (within 30 days of initiation of study treatment) or is anticipating concurrent use of an investigational drug or device.

29. Subject has a condition or a situation which, in the investigator's opinion, might put the subject at increased risk, confound the study data or interfere significantly with the subject's study participation.

30. Subject would be wearing contact lens in either eye during the dosing period of Day -1 to Day 14.

31. Subject is taking a medication that the investigator feels might interfere with the study parameters.

32. Subject tests positive for the COVID-19 virus prior to Visit 1 (Day -14 to Day -2).

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 and the labeling of subject numbers according to a validated SAS® computer-generated randomization list. The study drug will be identified as a new drug, limited by Federal law to investigational use, manufactured and packaged for Surface Pharmaceuticals.

Subjects will be randomly assigned to receive masked study drug (either 0.2% BSP ophthalmic solution or vehicle) for 16 days BID. Subjects will receive instructions for dosing at home and for completing a dosing and pain assessment diary during the study dosing phase (Day -1 to Day 14).

During the 16-day dosing period, a total of 32 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).

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-201 based on marketed ophthalmic corticosteroids include the following:

- Prolonged intensive use of corticosteroids may result in intraocular pressure (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-201 is unlikely to lead to any serious adverse effects.

Drug-Drug Interactions: No topical ophthalmic drug-drug interactions are known for SURF-201. Corticosteroids (including betamethasone) 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-201 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:

- Any corticosteroid at least 15 days before surgery and throughout the duration of the study;
- Depot-corticosteroids in either eye at least 45 days before surgery and throughout the duration of the study;
- Administration of any nonsteroidal anti-inflammatory drugs (NSAIDs) including but not limited to topical, systemic (including sleep-aids containing NSAIDs), inhaled, or irrigation solution at least 1 week before surgery and throughout the duration of the study, with the exception of aspirin, where oral doses of 165 mg/day or lower are allowed;
- Ocular or systemic antihistamines (including sleep-aids containing an antihistamine), or mast cell stabilizers in either eye at least 1 week before surgery and throughout the study's dosing period;
- Triamcinolone in either eye at least 90 days before surgery and throughout the study's dosing period;
- Medications used to treat benign prostatic hyperplasia throughout the duration of the study;
- Inhaled, ingested, sublingual, transdermal or topical products containing marijuana, tetrahydrocannabinol (THC) or cannabidiol (CBD) at least 1 week before surgery and throughout the study's dosing period and for one day after the study's dosing period ends;
- Systemic pain relievers, analgesics (e.g., pregabalin, gabapentin, opioids) 14 days before surgery and throughout the duration of the study;
- 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.

During the study dosing period (Day -1 through Day 14), if the investigator determines that a rescue medication is necessary due to lack of efficacy (whether at a planned study visit or at an unscheduled visit), the subject should be discontinued from the study drug and the appropriate rescue medication prescribed. The subject should continue to be seen for all remaining study visits to assess safety and efficacy. This information must be recorded in the subject's source record and on the appropriate eCRF.

8. CLINICAL ASSESSMENTS/EXAMINATION PROCEDURES

The ophthalmic examinations listed below will be conducted in the surgery eye (study eye) and in the order specified. The fellow eye (non-study eye) may be examined at the investigators' discretion.

Subject Assessment of Pain via Diary: Surgery eye (study eye) pain will be evaluated prior to each study drug dose using a pain scale included in the dosing and pain assessment diary that subjects complete at home.

Investigator Assessments include the following:

Visual Analog Scale (VAS) (ocular symptoms): Eye pain/discomfort will be evaluated at Screening Visit 1 (Day -14 to Day -2) and at Visit 3 through Visit 7 (Day 1 through Day 32) using a VAS, scoring from 0 to 100 using a mark on a 100 mm line (0 = absent; 100 = maximum).

Best-Corrected Visual Acuity (BCVA): BCVA will be measured at Screening Visit 1 (Day -14 to Day-2) and at Visit 3 through Visit 7 (Day 1 through Day 32) (log of the minimum angle of resolution [logMAR] score using ETDRS [Early Treatment Diabetic Retinopathy Study] chart will be used to measure BCVA). A pinhole test may be performed at Visit 3 (Day 1).

Biomicroscopy: Slit lamp biomicroscopy, including the evaluation of anterior chamber cell (ACC) and anterior chamber flare, chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates will be conducted by a board-certified ophthalmologist at Screening Visit 1 (Day -14 to Day -2) and at Visit 3 through Visit 7 (Day 1 through Day 32).

Ophthalmoscopy: Ophthalmoscopy will be performed at Screening Visit 1 (Day -14 to Day-2) and Visit 5 (Day 15) by a board-certified ophthalmologist. Ophthalmoscopy will be performed at Visit 7/Early Discontinuation Visit only if not performed at Visit 5.

Intraocular Pressure (IOP): IOP will be measured at Screening Visit 1 (Day -14 to Day-2) and at Visit 3 through Visit 7 (Day 1 through Day 32) in mmHg using a Goldmann applanation tonometer.

Standard examinations for subjects undergoing cataract surgery will be conducted by the investigator or qualified designated staff. However, ophthalmoscopy and biomicroscopy examinations will be performed by the same board-certified ophthalmologist who performs a subject's cataract surgery. All ratings and procedures should be performed by the same examiner from visit to visit whenever possible.

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 5 (Day 0 through Day 15), subjects' diaries will be reviewed and compliance with study drug dosing and completion of pain assessments will be evaluated.

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 the study eye (surgery eye)
- 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 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 case report form as an AE.

IOP: An increase from baseline or any prior study visit of 10 millimeters of mercury (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: Anterior chamber cell and flare, chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates will be assessed in the study. Since the severity of these assessments will be recorded and carefully monitored during the study, worsenings do not need to be recorded as AEs unless the investigator judges it appropriate. Any treatment-emergent findings (i.e., findings that were not present prior to treatment or a worsening relative to the pretreatment baseline) outside of these assessments 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.

VAS: Pain/discomfort will be assessed in the study eye. Since the severity of these assessments will be recorded and carefully monitored during the study, worsenings do not need to be recorded as AEs unless the investigator judges it appropriate.

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 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 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 efficacy endpoint will be the proportion of subjects with ACC grade of 0 (cell count=0) at Day 15. Subjects with an ACC grade of >0 at Day 15 or who receive rescue medication prior to Day 15 will be treated as failures. Last-observation-carried-forward (LOCF) will be used for the intent-to-treat (ITT) analysis.

Secondary Efficacy Endpoint: The secondary efficacy endpoint is the proportion of subjects who achieve a pain score of 0 at each post-surgical VAS (0-100 millimeter [mm] scale) assessment (Days 1, 8, 15, 22 and 32).

Safety Variables: AEs, BCVA, IOP, 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 will include all randomized subjects who undergo routine uncomplicated unilateral cataract surgery. Subjects in the ITT population will be analyzed in the treatment group to which they were assigned by the randomization scheme, regardless of which study drug they receive.

Per Protocol Population: The per-protocol (PP) population will include all subjects in the ITT population who have no major protocol deviations during the study.

10.4. Data Handling: Handling of Missing Data

The primary efficacy analysis for the ITT population will use the LOCF method to impute missing observations due to COVID-19 or otherwise [EMA. Guideline on Missing Data in Confirmatory Clinical Trials [Internet]. 2010. Available from: https://www.ema.europa.eu/en/missing-data-confirmatory-clinical-trials].

Partial dates and missing dates will not be imputed. Any classifications based on partial or missing dates will assume a "worse case" scenario. If a medication cannot be classified as either prior or concomitant due to missing or partial start and stop dates, it will be considered to be concomitant. If an AE cannot be classified as resolved prior to the end of the study period due to missing or partial stop dates, it will be assumed to be ongoing.

10.5. Statistical Methods: General Principles

All data processing, summarization and analyses will be performed using Sponsor designee's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package. The principles that will be applied to all tables, listings and figures (TLFs) unless otherwise stated are outlined in Table 1.

Table 1: Principles for All TLFs

Principle	Value
Baseline	Defined as the last measurement taken prior to dosing (Day -14 to Day -2).
Significant tests	Two-sided and use a 5% significance level for main effects and 10% significance level for interaction terms.
Treatment group labels and order presented	SURF-201 Vehicle
Tables	Data in summary tables presented by treatment group, assessment and visit (where applicable).
Listings	All data collected presented by treatment group, site, subject number, and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects/observations (N), mean, standard deviation (SD), median, minimum (min) and maximum (max).
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	Number of subjects in the analysis population, unless stated otherwise
Include "Missing" as category	No, N will change, unless stated otherwise
Display for 0 percentages	-
Display to one more decimal place than collected value	Mean Standard Error Mean Difference Median
Display to two more decimal places than collected value	Standard Deviation Confidence Interval
Date Format	DD-MMM-YYYY

10.6. Efficacy

10.6.1. Primary Efficacy Analysis

The primary efficacy analysis will test for a difference in the proportion of subjects with ACC grade zero (0) in the SURF-201 active treatment group versus the vehicle group only at Day 15. An ACC grade of zero is considered to be a success, and an ACC grade >0 or the use of rescue medication prior to Day 15 is counted as a failure (as described in Section 3.1). Missing data will be imputed using LOCF in the ITT population only.

The test will be the z-test for proportions and will be reported with associated z-based 95% confidence interval (CI). The null hypothesis is that the proportions are equal, and this will be a two-sided test at the alpha = 5% level. If the assumptions of the z-test are not satisfied, a Barnard's exact test and exact 95% CIs will be presented.

10.6.2. Secondary Efficacy Analysis

The differences in the proportion of subjects who achieve a pain score of 0 on the VAS at each post-surgical assessment between SURF-201 and vehicle will be tested using a z-test for proportions with a 95% CI. The null hypothesis is that the proportions are equal, and this will be a two-sided test at the alpha = 5% level. If the assumptions of the z-test are not satisfied, a Barnard's exact test and exact 95% CIs will be presented.

10.7. Safety

10.7.1. Adverse Events

Adverse Events (AEs) will be summarized. To select events for summarization when there are multiple occurrences of an event for a subject, AEs will be sorted by severity and relationship to study drug (i.e., severity will be sorted as mild, moderate, and severe; relationship will be sorted as not related and related).

Adverse Events (AEs) will be coded according to MedDRA version 23.0 Update. All data will be listed and summarized in the safety population.

Treatment emergent AEs (TEAEs) will be defined as AEs that first occurred or worsened on or after the date of first dose of study drug. Treatment emergent SAEs (TESAEs) will be defined as SAEs that first occurred or worsened on or after the date of first dose of study drug.

Adverse event (AE) summaries will be provided for the number of subjects experiencing at least one event overall and in each treatment group. This will be provided for all AEs, TEAEs, SAEs and TESAEs. All will be presented overall and divided into ocular and non-ocular AEs where ocular events are defined as those where an eye is indicated in the eCRF form. Percentages for the subject based summaries will be calculated based on the number of subjects in the safety population.

Incidence of Adverse Events (AEs): The per subject incidence of TEAEs for each system organ class (SOC) and preferred term (PT) will be summarized. If a subject reports the same PT multiple times, then that subject will only be counted once for that PT. As with the PT, if a subject reports multiple TEAEs within the same system organ class, then the subject will only be counted once for that system organ class. Summaries will be further divided by ocular and non-ocular.

Relationship of Adverse Events (AEs) to the Study Drug: An overall summary of AEs by relationship to the study drug will be presented separately for each treatment group. The relationships indicate the possibility that the study drug caused the event. The possible grades of relationships are “Not Related” and “Related”. If a subject reports multiple occurrences of the same AE, only the most strongly related occurrence would be presented for all subject level summaries. The per subject incidence of TEAEs related to study drug for each SOC, and PT for AEs related to study drug will be summarized.

Severity of Adverse Events (AEs): An overall summary of AEs by severity will be presented separately for each treatment group. If a subject reports multiple occurrences of the same AE, only the most severe event will be presented for all subject level summaries. The order of severity will be “Mild,” “Moderate,” and “Severe”. The per subject incidence of severe TEAEs for each SOC, and PT will be summarized. Percentages will be calculated based on the number of subjects in the safety population.