1 TITLE/SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN

Protocol Number: NVU-003

Title: A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease associated with Meibomian Gland Dysfunction (Gobi Study)

Study Phase: 3

Sponsor: Bausch & Lomb, Incorporated
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SAP Version History/Summary of Changes

Version/Date	Summary of Changes
1.0	Initial Issuance of Document

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Terms or Abbreviations	Definitions
AE	Adverse event
AICc	Akaike information criterion with a correction for finite sample sizes
ATC	Anatomic Therapeutic Class
BCVA	Best-corrected visual acuity
BOCF	Baseline observation carried forward
cCFS	Central Corneal Fluorescein Staining
CFB	Change from baseline
eCRF	Electronic case report form
CRO	Clinical Research Organization
CS	Clinically significant
CSR	Clinical Study Report
DED	Dry Eye Disease
eCRFs	Electronic Case Report Forms
ET	Early termination
ETDRS	Early Treatment of Diabetic Retinopathy
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigation medicinal product
IOP	Intraocular pressure
IRB	Institutional Review Board
IRS	Interactive Response System
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
MGD score	Meibomian Gland Assessment
NCS	Not clinically significant
NEI	National Eye Institute
OD	Oculus Dexter (Right eye)

Terms or Abbreviations	Definitions
OS	Oculus Sinister (Left eye)
OSDI	Ocular Surface Disease Index
OU	Oculus Uturque (Both eyes)
PPS	Per Protocol Set
PT	Preferred term
QID	4 times daily
SAF	Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TFBUT	Tear Film Break Up Time
tCFS	total Corneal Fluorescein Staining
VA	Visual acuity
VAS	Visual analogue scale
WHODrug	World Health Organization Drug Dictionary

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to frame the analyses and summarization of the clinical data from the trial "A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease associated with Meibomian Gland Dysfunction (Gobi Study)".

The content and structure of this SAP provide sufficient detail to meet the requirements identified by the United States Food and Drug Administration (FDA) as outlined in the "E9 Statistical Principles for Clinical Trials," revised as of September 1998, and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: *Guidance on Statistical Principles in Clinical Trials.*

The following documents were used in the preparation of this SAP:

- Protocol NVU-003, Version 3.0, 16 March 2020
- Electronic case report forms (eCRFs) for Protocol NVU-003 (dated 22 May 2020)

The following CDISC standards will be used for the analysis and summarization outlined in this SAP:

Exchange Standards	SDTM 1.7 / SDTM IG v3.3 ADaM 2.1 / ADaM IG v1.2 **Define.xml v2.0**
Terminology Standards	CDISC SDTM 2018-02-20 CDISC ADaM 2019-10-03 MedDRA v22.1 WHODRUG B3 GLOBAL (SEPT 2019)

The SAP provides details of the protocol-specified analyses of efficacy and safety that will be completed in support of the clinical study report (CSR) for Protocol NVU-003. Changes made to the SAP after finalization, but before database lock and unmasking, will be documented in an amendment and the changes summarized at the beginning of this document. Any deviations from these guidelines will be documented in the CSR. Any post hoc or unplanned analyses will also be identified as such if they are included in the CSR.

The trial will be multi-center, randomized, double-masked, and saline-controlled for evaluating the efficacy, safety, and tolerability of NOV03 (perfluorohexyloctane) ophthalmic solution in comparison to a saline control for the treatment of the signs and symptoms of Dry Eye Disease [redacted]

To demonstrate efficacy (superiority of NOV03 to saline) in two primary endpoints, change from baseline (CFB) in total Corneal Fluorescein Staining (tCFS) (National Eye Institute

(NEI) scale) at Day 57 and CFB in Dryness Score (visual analogue scale [VAS] Severity of Dryness) at Day 57, a hierarchical fixed sequence testing will be employed to maintain type I error rate.

Using the Full Analysis Set (FAS), the difference in the mean CFB of tCFS at Day 57 between treatments will be tested first. If the test of the difference (NOV03 minus saline) is statistically significant at the 0.05 significance level and in favor of NOV03 (difference less than 0), NOV03 will be declared to be superior to saline in the mean CFB of tCFS, the trial will be considered a success, and the difference in the mean CFB of Dryness Score (VAS Severity of Dryness) at Day 57 between treatments using FAS will also be tested.

If in addition to a statistically significant test of the difference in the mean CFB of tCFS at Day 57 which is in favor of NOV03, the test of the difference in the mean change from Dryness Score (VAS Severity of Dryness) at Day 57 is also statistically significant at 0.05 significant level and in favor of NOV03, then NOV03 will be declared to be superior to saline in both the mean CFB of tCFS and the mean CFB of Dryness Score (VAS Severity of Dryness) at Day 57.

- **Masking** - This is a double-masked trial (NCI Preferred Term 'Double Blind Study'). The subjects, investigators, Clinical Research Organization (CRO) personnel involved in conduct and monitoring of the trial and sponsor will be masked with respect to the investigational medicinal product (IMP) assignment. Due the physicochemical differences between NOV03 and saline, there will be a dedicated dosing coordinator who will be responsible for the handling of IMP and activities (such as dispensation, collection, and accountability) surrounding the use of IMP. This designee shall not participate in any other trial procedures and shall not report this information to other staff. The investigational drug and control will be provided in identical bottles and labels to ensure the double-masked character of the trial. Subjects will be instructed to administer the IMP out of the sight of the Investigator or site staff other than the dedicated dosing coordinator and are not to discuss IMP characteristics and/or their experience with the IMP.

- **Treatment assignment method** - Subjects who meet all inclusion and exclusion criteria at Visits 0 and 1 will be randomized to a treatment group NOV03 (100% perfluorohexyloctane) or saline (0.6% sodium chloride solution) in a 1:1 ratio stratified by clinical site and dryness score <70 vs ≥ 70 (VAS) at baseline (Visit 1). Subjects who fail to qualify for the trial at screening may be rescreened (see Section 6.2).

  An Interactive Response System (IRS) will be used to account for the stratification factors while assigning the drug kit numbers at Visits 1, 2 and 3. Each treatment group of this trial will consist of approximately 280 subjects, such that approximately 250 evaluable subjects per arm complete the trial, for an estimated total of 560 randomized subjects. Specifically, the treatments are defined as follows:

- Treatment 1: NOV03 (100% perfluorohexyloctane), 4 times daily (QID)
- Treatment 2: Saline (0.6% sodium chloride solution), QID

- **Packaging and labeling** - The IMP will be labelled according to the legal requirements and packaged into individual subject kits, each containing 2 bottles of NOV03 or saline solution. In compliance with the Code of Federal Regulations 21 part 312, section 312.6, the labels for the IMP shall be comprised of:

  - Protocol number
  - Kit number
  - Investigational new drug statement
  - Storage conditions
  - Name and address of the sponsor

- **Trial configuration** - This is a parallel trial design (NCI Preferred Term 'Parallel Study'). Subjects will be randomized to either NOV03 QID or saline QID in a 1:1 ratio. Subjects will self-administer one drop of masked investigation product in the lower cul-de-sac of each eye QID at approximately the same time e.g., morning, lunch time/midday, afternoon/early evening, and at bedtime. ***Note***: if a dose is missed, the next dose should be administered on time.
- **Type of control used** - This is a saline-controlled (NCI Preferred Term 'Placebo Control'), superiority trial.
- **Duration of the trial** - The estimated trial duration is approximately 8 months, from first subject first visit to last subject last visit. An individual subject's participation will involve 5 visits over approximately a 10-week period, including screening. After the trial, subjects will be treated according to standard of care, at the discretion of the treating physician.

  Subjects who complete trial NVU-003 without major protocol deviations and have been compliant with NVU-003 trial procedures and application of IMP may be invited to enroll into trial NVU-004. NVU-004 will be a 12-month open-label safety extension trial of NVU-003 to assess the safety of topical NOV03 for the treatment of DED.
- **Number of clinical sites and countries involved** - Approximately 26 clinical sites in the United States will randomize approximately 560 (280 in each treatment group) subjects.
- **Interim analyses** - No interim analyses are planned for this trial.
- **Power** - A true difference in the mean CFB of tCFS score at Day 57 of -1.0 (NOV03 minus saline) with a common standard deviation of 2.8, and a true difference in the

mean CFB of Dryness Score (VAS Severity of Dryness) at Day 57 of -10 (NOV03 minus saline) with a common standard deviation of 28 were assumed for the sample size calculation. To demonstrate superiority of NOV03 over saline in the mean CFB of tCFS score at Day 57 with a two-sided alpha of 0.05 and superiority of NOV03 over saline in the mean CFB of Dryness Score (VAS Severity of Dryness) at Day 57 with a two-sided alpha of 0.05, *a minimum number of 250 FAS subjects (study eyes) per treatment group* will be needed to achieve 95.8% power assuming independence between tCFS score and Dryness Score (VAS Severity of Dryness). A positive correlation between these two endpoints would increase the overall power.

Accounting for an assumed 10% subject discontinuation rate, approximately 560 subjects (280 subjects each arm) will be randomly assigned to trial treatment such that approximately 250 evaluable participants per arm complete the trial.

5 TRIAL OBJECTIVES

5.1 Primary Objective

The primary objective of this trial is to assess the efficacy of NOV03 (perfluorohexyloctane) ophthalmic solution at a QID dosing regimen in comparison to a saline control for the treatment of the signs and symptoms of DED [redacted]

The population-level summaries of the primary estimands are:

- Difference in mean CFB of tCFS score (NEI scale) at Day 57 (NOV03 minus saline)
- Difference in mean CFB of Dryness Score (VAS Severity of Dryness) at Day 57 (NOV03 minus saline)

5.2 Secondary Objectives

The secondary objective of this trial is to assess the safety and tolerability of NOV03 (perfluorohexyloctane) ophthalmic solution at a QID dosing regimen in comparison to a saline control in subjects with DED [redacted] This will be evaluated by monitoring ocular and non-ocular adverse events (AE), visual acuity, slit-lamp biomicroscopy, intraocular pressure, dilated fundoscopy, instillation comfort questionnaire, and eyedrop acceptability questionnaire.

Further objectives of this trial are to explore the effect on other efficacy endpoints of NOV03 (perfluorohexyloctane) ophthalmic solution at a QID dosing regimen in comparison to a saline control in subjects with DED [redacted]

- CFB of Dryness Score (VAS) at Day 15
- CFB in tCFS (NEI scale) at Day 15
- CFB of VAS burning/stinging at Day 29
- CFB in cCFS (NEI scale) at Day 57
- CFB of Dryness Score (VAS) at Day 29

- CFB in CFS central and inferior sub-regions (NEI scale) to each measured post-baseline visit
- Proportion of tCFS responders (≥3 improvement based on NEI scale) at Day 57
- Proportion of Dryness Score responders (≥30% improvement from baseline) at Day 57
- CFB in VAS burning/stinging, sticky feeling, foreign body sensation, itching, blurred symptoms at each measured post-baseline visit
- CFB in Ocular Surface Disease Index (OSDI) at each measured post-baseline visit

[redacted]

6 INVESTIGATIONAL PLAN

6.1 Overall Trial Design

NVU-003 is a phase 3, multi-center, randomized, double-masked, saline-controlled trial to evaluate the effect of NOV03 (100% perfluorohexyloctane) at a QID dosing regimen on signs and symptoms of Dry Eye Disease. Approximately 560 male and female subjects (280 each arm) of at least 18 years of age with a subject-reported history of DED in both eyes and who meet all other trial eligibility criteria will be randomized, stratified by clinical site and dryness score <70 vs ≥ 70 (VAS) at baseline, 1:1 to receive 1 of 2 treatments:

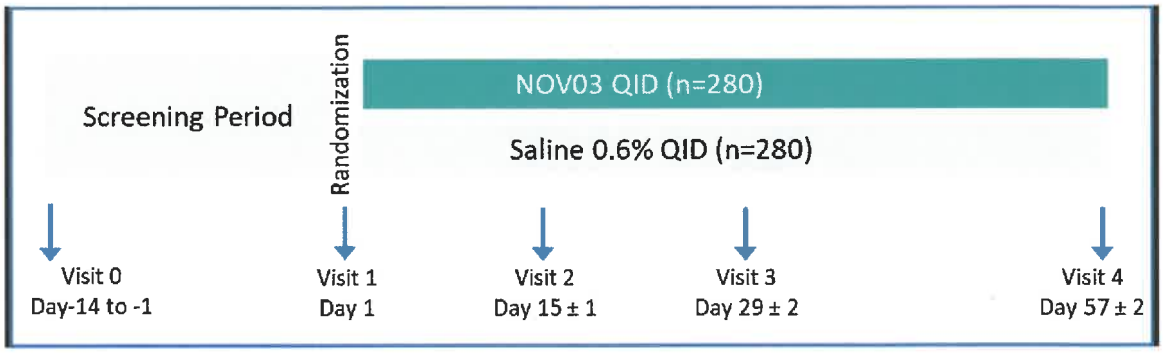
- Treatment 1: NOV03 (100% perfluorohexyloctane), 4 times daily (QID)
- Treatment 2: Saline (0.6% sodium chloride solution), QID

Each treatment group will be composed of 280 subjects such that approximately 250 evaluable subjects per arm complete the trial. Approximately 26 clinical sites are anticipated to participate.

This trial will consist of two periods: a screening period of one to 14 days and a 57-day treatment period.

6.1.1 Trial Design Diagram

Figure 1: Trial Design Schematic



6.1.2 Trial Procedures

The schedule of assessments, as outlined in the trial protocol, is presented below in Table 1.

Table 1. Schedule of Assessments

Procedure	Visit 0 Within 14 days before Visit 1 (Day -14 to -1)	Visit 1 Day 1	Visit 2 Day 15 ± 1	Visit 3 Day 29 ± 2	Visit 4 /(ET) Day 57 ± 2
Informed Consent / HIPAA	X				
Demographics	X				
Medical/Surgical History	X	X			
Previous/Concomitant Medication	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X			
Urine Pregnancy Test	X	X			X
Eyedrop Acceptability Questionnaire					X
Dryness Score (VAS severity of dryness)*		X	X	X	X
VAS*		X	X	X	X
OSDI*	X	X	X	X	X
Eyedrop Acceptability Questionnaire*					X
Visual Acuity (ETDRS)	X	X	X	X	X
Slit-Lamp Biomicroscopy	X	X	X	X	X
TFBUT*	X	X			X
Corneal Fluorescein Staining (NEI scale)*	X	X	X	X	X
Meibomian Gland Assessment (MGD score)*	X	X			X
Schirmer's Test I (without anesthesia)*	X	X			X
Intraocular Pressure	X				X
Dilated Fundoscopy	X				X
Randomization (via IRS)		X			
In-office instillation of randomized IMP		X			
Instillation Comfort Questionnaire		X			
Adverse Event Query	X	X	X	X	X
Dosing Diary Dispensation and/or Review		X	X	X	X
Dispensation of trial medication		X	X	X	

Procedure	Visit 0 Within 14 days before Visit 1 (Day -14 to -1)	Visit 1 Day 1	Visit 2 Day 15 ± 1	Visit 3 Day 29 ± 2	Visit 4 /(ET) Day 57 ± 2
Collection of trial medication			X	X	X
Trial Exit					X

*=Assessment to be conducted in the order as depicted in the Schedule of Assessments; ETDRS = Early Treatment of Diabetic Retinopathy Study; HIPAA = Health Information Portability and Accountability Act; NEI = National Eye Institute; OSDI = Ocular Surface Disease Index; TFBUT = Tear Film Break Up Time;
ET = Early Termination; VAS: burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms

6.2 Selection of Trial Population

All subjects must be at least 18 years of age, of either gender and of any race. Subjects must have a reported history of dry eye in both eyes and meet all inclusion criteria and none of the exclusion criteria.

If the subject does not qualify at Visit 0 or Visit 1, he or she may be re-screened once after 14 days from the relevant visit provided that new informed consent to be signed, new subject number received via IRS and all the assessments are repeated as per protocol requirements.

Key inclusion and exclusion criteria are detailed below. Full details can be found in the protocol.

6.2.1 Inclusion Criteria

1. Be at least 18 years of age at the time of consent.
2. Provide written informed consent.
3. Have a subject reported history of Dry Eye Disease in both eyes for at least 6 months prior to Visit 0.
4. Have TFBUT $\leq$5 sec at Visit 0 and Visit 1.
5. Have OSDI $\geq$25 at Visit 0 and Visit 1.
6. Have an unanesthetized Schirmer's Test I $\geq$5 mm at Visit 0 and Visit 1.
7. Have MGD defined as total MGD score $\geq$ 3 (secretion of 5 central glands on lower eyelid will be evaluated, each will be scored from 0-3; 0 = normal, 1 = thick/yellow, whitish, particulate 2 = paste; 3 = none/occluded; total score will range from 0-15) at Visit 0 and Visit 1.
8. Have a total corneal fluorescein staining score of 4$\leq$ X $\leq$11 (i.e. sum of inferior, superior, central, nasal, and temporal) according to the NEI scale at Visit 0 and Visit 1.
9. Have at least one eye (the same eye) satisfy all criteria for 4, 6, 7, and 8 above at Visit 0 and Visit 1.
10. Be able and willing to follow instructions, including participation in all trial assessments and visits.

6.2.2 Exclusion Criteria

1. Have been randomized in NVU-002.
2. Have any clinically significant ocular surface slit-lamp findings at Visit 0 and Visit 1 and/or in the opinion of the investigator have any findings that may interfere with trial parameters and may include eye trauma or history of eye trauma.
3. Have a history of Stephen Johnson Syndrome.
4. Have active blepharitis or lid margin inflammation that required any topical antibiotics or topical steroids within last 30 days prior to Visit 0 or will require such treatment during the trial. Any other lid margin therapy such as lid scrubs, lid wipes, warm compresses, systemic antibiotics and oral supplements for treatment of ocular conditions or oral supplements had to be stable within the last 30 days prior to Visit 1 and should be maintained stable throughout the trial.

5. Have had a LipiFlow procedure or any kind of other procedures affecting meibomian glands within 6 months prior to Visit 1.
6. Have abnormal lid anatomy that causes incomplete eyelid closure including entropion and ectropion or floppy lid syndrome that exposes parts of the conjunctiva or impairs the blinking function of the eye.
7. Have received or removed a permanent punctum plug within 3 months (6 months for dissolvable punctum plugs) prior to Visit 1 or expected to receive a punctum plug or removal of a punctum plug, or a punctum plug expected to be dissolved during the trial.
8. Have Dry Eye Disease secondary to scarring, irradiation, alkali burns, cicatricial pemphigoid, or destruction of conjunctival goblet cells (as with vitamin A deficiency).
9. Have an ocular or periocular malignancy.
10. Have a corneal epithelial defect; have significant confluent staining or filaments anywhere on the cornea.
11. Have a history of herpetic keratitis.
12. Have active ocular allergies or ocular allergies that are expected to be active during the trial period.
13. Be diagnosed with an ongoing ocular or systemic infection (bacterial, viral, or fungal), including fever and current treatment with antibiotics.
14. Have worn contact lenses within 1 month of Visit 0 or anticipate using contact lenses during the trial.
15. Have used any eye drops and/or TrueTear™ device (Intranasal Tear Neurostimulator) within 24 hours before Visit 1.
16. Have had intra-ocular surgery or ocular laser surgery within the previous 6 months or have any planned ocular and/or lid surgeries over the trial period.
17. Be a family member living in the same household of another randomized NVU-003 subject.
18. Be a clinical site employee that is directly involved in the management, administration, or support of this trial or be an immediate family member of the same.
19. Be a woman who is pregnant, nursing or planning a pregnancy.
20. Be unwilling to submit to a urine pregnancy test at Visit 0, Visit 1 and Visit 4 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy) or is post-menopausal (without menses for 12 consecutive months).
21. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the trial, she must agree to use adequate birth control as defined above for the remainder of the trial.
22. Have an uncontrolled systemic disease in the opinion of the investigator.

23. Have a known allergy and/or sensitivity to the investigational drug or saline components.
24. Have active ocular or periocular rosacea that in the judgement of the investigator interferes with the trial (e.g., clinically relevant lid induration).
25. Have pterygium in any eye.
26. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 60 days of Visit 1.
27. Have used any topical steroids treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0.
28. Have used any oral medications known to cause ocular drying (e.g. antihistamines, antidepressants, etc.) on a non-stable regimen within 1 month prior to Visit 0 or expected to be unstable during the trial.
29. Have a corrected visual acuity worse than or equal to logarithm of the minimum angle of resolution (logMAR), +0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 0 and Visit 1.
30. Have a condition or be in a situation (including language barrier) which the investigator feels may put the subject at significant risk, may confound the trial results, or may interfere significantly with the subject's participation in the trial.

6.3 Treatments

6.3.1 Investigational Medicinal Product(s)/ Formulation(s)

NOV03 drug product is a thin, clear, preservative-free ophthalmic solution drop (see Table 2). Saline eye drops preserved with benzalkonium chloride will be supplied as the control product (see Table 3). Investigational drug and control will be provided in identical bottles and labels to ensure the double-masked character of the trial.

Table 2. Active Investigational Product

	Investigational Product
Product code:	NOV03
Chemical name:	Perfluorohexyloctane
Molecular formula:	$C_{14}H_{17}F_{13}$
Dosage form:	3 mL ophthalmic solution
Unit dose	11 µL drop size; 100% perfluorohexyloctane
Route of administration	Topical ocular administration
Physical description	Colorless and clear ophthalmic solution
Excipients:	None
Manufacturer:	[redacted]

Table 3. Control/Reference Investigational Product

	Control/Reference Investigational Product
Product name:	Saline solution

Chemical name:	Sodium chloride solution (0.6 %)
Molecular formula:	NaCl
Dosage form:	3 mL ophthalmic solution
Unit dose	35-40 µL drop size
Route of administration	Topical ocular administration
Physical description	Colorless and clear ophthalmic solution
Excipients:	0.01% benzalkonium chloride w/v
Manufacturer:	[redacted]

6.3.2 IMP Dispensation

- The dedicated dosing coordinator is responsible for dispensing the IMP and supervision of the first dose administration at Visit 1.
- The IMPs must only be distributed to subjects properly qualified under this protocol to receive IMP.
- IMP will be provided to the clinical sites as subject kits containing 2 bottles of NOV03 or saline solution.
- At the end of Visit 1, qualified subjects will be randomized and a kit of IMP containing 2 bottles for each subject will be assigned using IRS. The first dose of IMP will be administered at the clinical site.
- At Visits 1 and 2 the subject will receive one subject kit.
- At Visit 3 the subject will receive two subject kits (total of 4 bottles).
- At Visits 2, 3 and 4 used/unused IMP will be collected from subjects for drug accountability.

Subjects will be instructed to immediately contact the site if there is any problem with the IMP, e.g. kit/bottle(s) was damaged or lost or if the open bottle was dropped. In case the subjects needs a replacement bottle of IMP, the next bottle from the kit can be used by the subject. If no bottle remains in the kit, a new kit will be assigned to the subject using IRS.

6.3.3 Instructions for Use and Administration

At Visit 1 subjects will be instructed by the dedicated dosing coordinator on appropriate hygiene and eye drop dosing technique for multiple use drops. Subjects will self-administer NOV03 or saline eye drops in each lower cul-de-sac of each eye under the supervision of the dedicated dosing coordinator on Day 1 (Visit 1). Subsequent eye drops on Day 1 are to be instilled by the subjects according to detailed written instructions. Subjects will be instructed to instill their drops into both eyes QID (e.g., morning, lunch time/mid-day, afternoon/early evening, and at bedtime) for the duration of the trial. If a dose is missed, then the next dose should be administered on time.

Dosing should be continued until the morning of the next Visit (should be at least 2 hours before first ophthalmic examination).

The bottles are designed for multiple use. Subjects will be instructed to only open one bottle at a time. They should be instructed not to discard the empty bottles but keep them in the kit

box and return them at their next visit in the kit box. Subjects will record in their dosing diary that their doses were taken. Subjects will be instructed not to show the assigned IMP to the Investigator or site staff other than the dedicated dosing coordinator, unless instructed to do so.

6.4 Efficacy and Safety Variables

6.4.1 Efficacy Variables

6.4.1.1 Primary Efficacy Endpoints

Two primary endpoints will be tested in the following order using hierarchical fixed sequence testing:

1. Change from baseline (CFB) in tCFS (NEI scale) at Day 57
2. CFB of Dryness Score (VAS Severity of Dryness) at Day 57

6.4.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated in the following order using hierarchical fixed sequence testing:

1. CFB of Dryness Score (VAS) at Day 15
2. CFB in tCFS (NEI scale) at Day 15
3. CFB of VAS burning/stinging at Day 57
4. CFB in central Corneal Fluorescein Staining (cCFS) (NEI scale) at Day 57

6.4.1.3 Other Pre-specified Efficacy Endpoints

1. CFB of Dryness Score (VAS) at Day 29
2. CFB in tCFS at Day 29
3. CFB in CFS central and inferior sub-regions (NEI scale) to each measured post-baseline visit
4. Proportion of tCFS responders (≥3 improvement based on NEI scale) at Day 57
5. Proportion of Dryness Score responders (≥30% improvement from baseline) at Day 57
6. CFB in VAS burning/stinging, sticky feeling foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms at each measured post-baseline visit
7. CFB in OSDI at each measured post-baseline visit

[redacted]

6.4.2 Safety Variables

1. Ocular and non-ocular AEs
2. logMAR visual acuity
3. Slit-Lamp biomicroscopy observations for lids, cornea, conjunctiva, anterior chamber, iris, and lens
4. Intraocular pressure
5. Dilated fundoscopy

[redacted]

6.5 Statistical Methods

6.5.1 Disposition of Subjects

Tabular summaries will be provided to summarize disposition for the Full Analysis Set (FAS), Per Protocol Set (PPS), and Safety Set (SAF). Reasons for screen failure will be summarized. Subjects included in each of the populations will be summarized overall and by level of stratification factor (clinical site and dryness score) by treatment group and overall. Reasons for exclusion from the analysis populations will be presented by treatment group and overall.

Subject disposition events including randomization, treated, completed study, prematurely discontinued study and/or treatment, and reasons for premature study and/or treatment discontinuation will be summarized by treatment group and overall.

6.5.1.1 Completed Subjects

A completed subject is one who is not a screen failure and has not been discontinued from the trial.

6.5.1.2 Discontinued Subjects

Notification of a subject discontinuation and the reason for study discontinuation will be made to the CRO and/or trial sponsor and will be clearly documented in the eCRF as:

- Adverse event
- Lack of efficacy
- Withdrawal by subject
- Protocol violation

- Lost to follow-up
- Death
- Other

Subjects who discontinue for any reason after randomization will not be replaced.

6.5.2 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and agreed to by the investigator. Deviations will be collected in the CRF. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria.

Major protocol deviations that could potentially affect the efficacy and result in removal from the PPS will be assessed and identified prior to database lock and unmasking. Major protocol deviations will be summarized by treatment and overall.

6.5.3 Data Sets Analyzed

Inclusion into the Full Analysis Set (FAS) and Safety Set (SAF) will be determined programmatically from the study data collected. Inclusion in the PPS will be determined programmatically from the eCRF data and a blinded Sponsor review.

The statistical analysis of safety data will be performed for the SAF. The analysis of baseline and efficacy data will be performed for the FAS. The primary efficacy analyses will also be performed on the PPS as sensitivity analyses.

A tabulation of the three analysis sets will presented by treatment and overall.

6.5.3.1 Full Analysis Set

The FAS includes all randomized subjects who received at least one dose of investigational product. The primary analysis will be performed on the FAS. Subjects in the FAS will be analyzed as randomized.

6.5.3.2 Per Protocol Set

The PPS includes subjects in the FAS who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PPS will be analyzed using observed data only for efficacy variables. Subjects in the PPS will be analyzed as treated.

6.5.3.2.1 Safety Set

The SAF includes all randomized subjects who have received at least one dose of the investigational product. The SAF will be analyzed for all safety assessments. Subjects in the SAF will be analyzed as treated.

6.5.4 Demographic and Other Baseline Characteristics

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The mean, median, and standard deviation will be presented with one more decimal place than the collected data and the minimum and maximum will be presented with the same decimal places as the collected data. The qualitative variables will be summarized using counts and percentages. All summaries will be presented by treatment group and overall in FAS, PPS, and SAF.

The following demographic and baseline characteristics will be summarized by treatment group and overall:

- Age (years)
- Age category (years) - <18, ≥18 to <65, ≥65
- Sex
- Race
- Ethnicity
- Iris color
- Eyes qualified for the study – right eye (OD), left eye (OS), both eyes (OU)
- Study Eye – OD, OS

Age will be calculated as (randomization date – date of birth) /365.25.

6.5.4.1 Baseline Ocular Assessments

Baseline ocular assessments will be summarized by treatment and overall for the FAS, PPS, and SAF.

6.5.4.1.1 Dryness Score

Baseline dryness score will be summarized using descriptive statistics by treatment group and overall. Assessment for both eyes is done simultaneously.

6.5.4.1.2 Visual Analog Scale (VAS)

Dry eye symptoms (sticky feeling, burning/stinging, foreign body sensation, itching, blurred vision, sensitivity to light, and pain), awareness of dry eye symptoms and frequency of dryness will be summarized using descriptive statistics by treatment group and overall. Assessment for both eyes is done simultaneously.

6.5.4.1.3 Ocular Surface Disease Index (OSDI)©

Baseline OSDI score will be summarized using descriptive statistics by treatment group and overall. Assessment for both eyes is done simultaneously. The OSDI questionnaire consists of 12 questions, with possible answers of 'All of the time', 'Most of the time', 'Half of the time', 'Some of the time' and 'None of the time'. To score the questionnaire, 'All of the time' is given a numerical value of 4, 'Most of the time' a value of 3, 'Half of the time' a value of 2, 'Some of the time' a value of 1, and 'None of the time' a value of 0. The OSDI score is calculated as:

$$\text{OSDI} = \frac{(\text{sum of scores}) \times 25}{(\#\text{ of questions answered})}$$

6.5.4.1.4 Best Corrected Visual Acuity (BCVA)

LogMAR Visual Acuity (VA) will be assessed in the right eye (OD). The procedure will be repeated for the left eye (OS). Subjects should use the most recent correction to attain their best-corrected visual acuity (BCVA). BCVA will be evaluated using the calculated logMAR score. Baseline BCVA of the study eye will be summarized using descriptive statistics by treatment group and overall.

6.5.4.1.5 Slit-Lamp Biomicroscopy

Lids, cornea, conjunctiva, anterior chamber, iris and lens for OD and OS will be examined. Observations will be graded as Normal, Abnormal CS (clinically significant) and Abnormal NCS (not clinically significant). Baseline slit-lamp biomicroscopy results of the study eye will be summarized using descriptive statistics by treatment group and overall.

6.5.4.1.6 Tear Film Break-Up Time (TFBUT)

For each eye, two measurements will be taken and TFBUT will be the average unless the two measurements are >2 seconds apart and are each <10 seconds, in which case, a third measurement would be taken and TFBUT will be the average of the two closest of the three. In all cases, only two values will be entered into the case report form. Baseline TFBUT of the study eye will be summarized using descriptive statistics by treatment group and overall.

6.5.4.1.7 Corneal Fluorescein Staining

Corneal fluorescein staining will be graded with the NEI Grading Scale. A standardized grading system of 0-3 is used for each of the five areas on each cornea. Grade 0 will be specified when no staining is present. The maximum total score for each eye is 15. Baseline corneal fluorescein staining of the study eye will be summarized using descriptive statistics by treatment group and overall.

6.5.4.1.8 Meibomian Gland Assessment (MGD Score)

The secretion of 5 central glands on the lower eyelid will be evaluated for each eye. Each of the 5 glands will be scored from 0-3: 0 = normal, 1 = thick/yellow, whitish, particulate; 2 = paste; 3 = none/occluded. The total score will thus range from 0-15. Baseline MGD score of the study eye will be summarized using descriptive statistics by treatment group and overall.

6.5.4.1.9 Unanesthetized Schirmer's Test I

Schirmer's Tear Test I will be performed ≥5 minutes after MGD evaluation. The length of the moistened area of the Schirmer test strip will be recorded (mm) for each eye. Baseline unanesthetized Schirmer's Test I of the study eye will be summarized using descriptive statistics by treatment group and overall.

6.5.4.2 Medical and Surgical History

Medical history, including ocular medical history, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 22.1 or higher). Non-ocular medical history will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall in the FAS. SOC will be sorted alphabetically. PT will be sorted by descending frequency overall within each SOC. Subjects with a particular medical history event or medical history class will be counted once at the PT level and once at the SOC level. Ocular medical history will be summarized at the subject and eye levels by treatment group and overall in the FAS with separate summaries for the study eye and fellow eye.

Surgical history will not be coded in this trial and thus all data as collected in the CRF will be provided in data listings. Data listings will be provided for medical history as well.

6.5.4.3 Concomitant Medications and Therapies

Concomitant medications will be coded to the Anatomical Therapeutic Chemical (ATC) classification levels 1-4 and preferred terms using the World Health Organization Drug Dictionary (WHODrug B3 Global Sept 2019).

Non-ophthalmic concomitant medications will be summarized by ATC Level 3 (therapeutic subgroup) and preferred term by treatment group and overall in the FAS. ATC Level 3 terms will be sorted alphabetically. Preferred terms will be sorted by descending frequency overall within ATC Level 3 term. Subjects receiving a particular medication or medication of ATC Level 3 will be counted once at the preferred term level and once at ATC Level 3.

Ophthalmic concomitant medications will be summarized at the eye level, separately for study and fellow eyes, and at the subject level by ATC Level 3 and preferred term by treatment group and overall in the FAS.

Concomitant therapies will not be coded in this trial and thus all data as collected in the CRF will be provided in data listings. Data listings will be provided for concomitant medications as well.

6.5.4.3.1 Concomitant Medications

A medication is considered concomitant if the start date is on or after the date of first dose of study drug or if the start date is prior to the first dose of study drug but the end date is after the date of first dose of the study drug. Partial dates will be imputed using the imputation rule specified in section 6.5.8.6.2. If the medication was started prior to first dose of study drug and the stop date is unknown or ongoing, the medication will be considered concomitant. If the start date or stop date is completely missing and it is unclear as to whether the medication is concomitant, the medication will be conservatively assumed as a concomitant medication.

6.5.4.3.2 Concomitant Therapies

A therapy is considered concomitant if the start date is on or after the date of first dose of

study drug or if the start date is prior to the first dose of study drug but the end date is after the date of first dose of the study drug. Partial dates will be imputed using the imputation rule specified in section 6.5.8.6.2. If the therapy was started prior to first dose of study drug and the stop date is unknown or ongoing, the therapy will be considered concomitant. If the start date or stop date is completely and it is unclear as to whether the therapy is concomitant, the therapy will be conservatively assumed as a concomitant therapy.

6.5.5 Measurements of Subject Dosing Compliance

The overall subject dosing compliance will be assessed using the data from the daily dosing diary eCRFs and will be summarized by treatment group in the SAF.

Subject dosing compliance is defined as the proportion of the number of doses administered out of the number of doses that should have been administered per protocol. On the first day of dosing, the expected number of doses will be based on the time of initial dose (24-hour clock) on the 'Dispense Investigational Product' form. If the initial dose in clinical occurs prior to 10:00, then four total doses should be administered that day (morning, lunch time/mid-day, afternoon/early evening, and at bedtime). If the initial dose in clinic occurs between 10:00 and 13:59, then three total doses should be administered that day (lunch time/mid-day, afternoon/early evening, and bedtime). If the initial dose occurs on or after 14:00, then two total doses should be administered that day (afternoon/early evening and bedtime). On the last day of dosing, if the time of last dose (24-hour clock) on the 'Visit Date' form is before 12:00, then only one dose should be administered that day. If the time of last dose (24-hour clock) is on or after 12:00 and before 14:00 then two total doses should be administered that day. If the time of last dose is on or after 14:00 then three total doses should be administered that day. If the last dose is not on the day of the visit, then the time of Dryness Score evaluation will be used to determine the expected number of doses. If the time of Dryness Score is after 12:00 and before 14:00, then only one dose should be administered that day. If the time of Dryness Score is on or after 14:00 and before 16:00, then two total doses should be administered. If the time of Dryness Score is on or after 16:00, then three total doses should be administered. The dosing compliance (%) will be calculated as (total number of doses administered/ total number of doses that should have been administered)*100.

In the event that the dosing diary is not returned, the total number of doses that should have been administered will be adjusted. The days with the dosing diary not returned will be excluded from the denominator. For example, if at Visit 2, 2 days are not returned, exclude those 2 days from the denominator and the number of doses that should have been administered will be adjusted from 56 to 48.

Compliance will be summarized using descriptive statistics in each treatment group and overall in the SAF. Compliance will be presented categorically by treatment group and overall:

- < 50%
- 50-<80%

- 80-<90%
- 90-100%
- >100%-120%
- >120%

6.5.6 Extent of Exposure

Exposure to study drug will be summarized in days. Exposure will be calculated as (last dose date – first dose date + 1). Duration of exposure will be summarized using descriptive statistics in each treatment group and overall in the SAF. Duration of exposure will be presented categorically:

- < 15 days
- 15-<29 days
- 29-<57 days
- ≥57 days

Dosing information for each treatment and each subject will be listed. Discontinuation of treatment will be summarized by treatment received. The primary reason for IMP discontinuation will also be summarized by treatment received.

6.5.7 Analysis of Efficacy

6.5.7.1 Descriptive Statistics

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The mean, median, and standard deviation will be presented with one more decimal place than the collected data and the minimum and maximum will be presented with the same decimal places as the collected data. The qualitative variables will be summarized using counts and percentages. Summaries will be presented by treatment group in the FAS and PPS.

All primary and secondary analyses will be two-sided at a significance level of 0.05.

6.5.7.2 Unit of Analysis

For efficacy endpoints, the unit of analysis will be the study eye as defined by the following:

Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the worst eye shall be chosen, and this will be defined as the eye with worse (higher) total corneal staining at Visit 1. If the total corneal staining is the same in both eyes then the right eye will be selected as the study eye.

6.5.7.3 Primary Efficacy Analyses

The primary comparisons in this trial will be between NOV03 versus saline at Day 57 in the FAS with available data per subject using the following estimands

- Endpoint:
  - CFB in tCFS in the study eye at Day 57
  - CFB of Dryness Score (VAS) at Day 57

- Intercurrent event:
  - Discontinuation of study medications is ignored. [treatment policy strategy]
  - Non-optimal compliance is ignored. [treatment policy strategy]
  - Withdrawal due to any reason. Missing data not imputed. [hypothetical strategy if overall study discontinuation rate is <5%]

- Population-level summary:
  - Difference in the mean CFB in tCFS in the study eye at Day 57 between NOV03 and saline
  - Difference in the mean CFB of Dryness Score (VAS) at Day 57 between NOV03 and saline

If the overall study discontinuation rate in the FAS is ≥5% then the primary analysis will be based on imputation methodology using the following estimands:

- Endpoint:
  - CFB in tCFS in the study eye at Day 57
  - CFB of Dryness Score (VAS scale) at Day 57

- Intercurrent event:
  - Discontinuation of study medications is ignored. [treatment policy strategy]
  - Non-optimal compliance is ignored. [treatment policy strategy]
  - Withdrawal due to lack of efficacy or adverse events: baseline observation carried forward (BOCF) is used to impute missing data [hypothetical strategy if overall study discontinuation rate ≥5%]
  - Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: multiple imputations using randomized treatment-based Markov Chain Monte Carlo (MCMC) is used to impute missing data [hypothetical strategy if overall study discontinuation rate ≥5%]

- Population-level summary:
  - Difference in the mean CFB in tCFS in the study eye at Day 57 between NOV03 and saline
  - Difference in the mean CFB of Dryness Score (VAS scale) at Day 57 between NOV03 and saline

The primary comparison in this trial will be between NOV03 versus saline at Day 57. The primary efficacy endpoints (e.g. CFB in total corneal fluorescein staining [NEI scale] and Dryness Score) will be tested using hierarchical fixed sequence testing and summarized descriptively (n, mean, standard deviation, median, min, and max) and analyzed separately using an ANCOVA model with terms for baseline value, and treatment.

Least squares mean for each treatment group and for the difference between treatment groups will be presented from each model together with two-sided p-values (used for primary inference) and 95% confidence intervals.

Sample SAS ANCOVA code:

```
PROC GLM DATA=INDATA;
  CLASS <TREATMENT>;
  MODEL <ENDPOINT>=<TREATMENT> <BASELINE>;
  LSMEANS <TREATMENT> / CL ALPHA=0.05;
  LSMEANS <TREATMENT> / PDIFF CL ALPHA=0.05;
RUN;
```

Additional robustness analyses will include repeating the primary analysis on the PPS; the FAS imputing missing data using last observation carried forward (LOCF); the FAS imputing missing data using MCMC multiple imputation methodology under different assumptions of missingness (at random and not at random) each using 30 imputed values.

Sample SAS MCMC MI (missing at random):

```
PROC MI DATA=INDATA SEED=97656 OUT=OUTDATA MINIMUM=0 MAXIMUM=3 ROUND=1
NIMPUTE=30;
  MCMC INITIAL=EM;
  BY <TREATMENT>;
  VAR <BASELINE> <PARAMETER>;
RUN;
```

Where <PARAMETER> has 5 levels and refers to the CFS for each region (inferior, superior, central, temporal, and nasal).

Sample SAS MCMC MI (not missing at random):

```
PROC MI DATA=INDATA SEED=36797 OUT=MDATA MINIMUM=0 MAXIMUM=3 ROUND=1
NIMPUTE=30;
  MCMC IMPUTE=MONOTONE;
  VAR <BASELINE> <PARAMETER>;
RUN;

PROC MI DATA=MDATA SEED=38549 OUT=OUTDATA2 MINIMUM=. 0 0 MAXIMUM=. 3 3
ROUND=. 1 1;
  CLASS <TREATMENT>;
  MONOTONE REG(<PARAMETER>=<BASELINE> / DETAILS);
  MNAR MODEL(<PARAMETER> / MODELOBS=(<TREATMENT>='Saline'));
  VAR <TREATMENT> <BASELINE> <PARAMETER>;
RUN;
```

Where <PARAMETER> has 5 levels and refers to the CFS for each region (inferior, superior, central, temporal, and nasal).

6.5.7.4 Secondary Efficacy

6.5.7.4.1 Secondary Efficacy Analyses

The following secondary endpoints will be tested hierarchically:

1. CFB in Dryness Score (VAS scale) at Day 15
2. CFB in tCFS (NEI scale) at Day 15
3. CFB in VAS burning/stinging at Day 57
4. CFB in cCFS (NEI scale) at Day 57

Inference will only be made on these endpoints, at a 2-sided alpha = 0.05, if both primary endpoints and any higher order secondary endpoints are statistically significant at a 2-sided alpha = 0.05 in favor of NOV03.

Quantitative secondary efficacy endpoints will be summarized similarly to the primary efficacy endpoints.

The primary analysis of the secondary endpoints will use the FAS with available data per subject, assuming the overall study discontinuation rate is <5%. If the overall study discontinuation rate is ≥5%, then the primary analysis of the secondary endpoints will be based on imputation methodology as defined in Section 6.5.7.3 and the available data analyses will become robustness analyses.

6.5.7.4.2 Other Pre-specified Efficacy Analyses

The other pre-specified efficacy analyses will use the FAS with available data per subject:

1. CFB of Dryness Score (VAS) at Day 29
2. CFB in tCFS at Day 29
3. CFB in CFS central and inferior sub-regions (NEI scale) to each measured post-baseline visit
4. Proportion of tCFS responders (≥3 improvement based on NEI scale) at Day 57
5. Proportion of Dryness Score responders (≥30% improvement from baseline) at Day 57
6. CFB in VAS burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms at each measured post-baseline visit
7. CFB in OSDI at each measured post-baseline visit

Quantitative efficacy variables will be summarized descriptively (n, mean, standard deviation, median, min and max) by visit, and analyzed similarly to the primary endpoint at each measured visit. Least squares mean for each treatment group and for the difference between treatment groups will be presented from the model together with two-sided p-values and 95% confidence intervals. For assessments performed by eye, study eye and fellow eye will be summarized separately.

Endpoints evaluating the proportion of study eyes (or subjects) meeting pre-defined criteria will be presented and tested between treatment groups using logistic regression analysis adjusting for baseline tCFS score at each measured follow-up visit.

Sample SAS logistic regression code:

```
PROC LOGISTIC DATA=INDATA DESCENDING;
  CLASS <TREATMENT>;
  MODEL <ENDPOINT>=<TREATMENT> <BASELINE>;
RUN;
```

6.5.7.6 Sensitivity Analyses

6.5.7.6.1 Sensitivity Analyses for Primary Efficacy Endpoints

Two-sample t-tests (equal variance assumed), Wilcoxon rank sum tests and mixed-effect repeated measures analysis comparing treatment groups will be performed as sensitivity analyses. The mixed-effect repeated measures model will include treatment, baseline value, visit, and the interaction between treatment and visit as fixed effects, and subject as a random effect. An unstructured covariance matrix will initially be used to model the covariance among repeated measures; however, if the model fails to converge using this covariance structure, either heterogeneous TOEPLITZ, homogeneous TOEPLITZ, or compound symmetry will be implemented according to the Akaike information criterion with a correction for finite sample sizes (AICc).

Sample SAS two-sample t-test code:

```
PROC TTEST DATA=INDATA;
  CLASS <TREATMENT>;
  VAR <ENDPOINT>;
RUN;
```

Sample SAS Wilcoxon rank sum test code:

```
PROC NPAR1WAY DATA=INDATA WILCOXON;
  CLASS <TREATMENT>;
  VAR <ENDPOINT>;
RUN;
```

Sample SAS mixed-effect repeated measures analysis code:

```
PROC MIXED DATA=INDATA;
  CLASS <TREATMENT> <VISIT>;
  MODEL <ENDPOINT>=<TREATMENT> <VISIT> <TREATMENT>*<VISIT> <BASELINE>;
  REPEATED <VISIT> / SUBJECT=<SUBJECT> TYPE=UN;
  RANDOM <SUBJECT>;
```

```
  ESTIMATE 'NOV03-SALINE' <TREATMENT> -1 1 / ALPHA=0.05 CL;
RUN;
```

Where 'Saline' is <TREATMENT>=0 and 'NOV03' is <TREATMENT>=1.

6.5.7.6.2 Sensitivity Analyses for Secondary Efficacy Endpoints

For quantitative secondary efficacy endpoints, two-sample t-tests, Wilcoxon rank sum tests and mixed-effect repeated measures analysis comparing treatment groups will be performed as sensitivity analyses.

The mixed-effect repeated measures model will include treatment, baseline value, visit, and the interaction between treatment and visit as fixed effects, and subject as a random effect. An unstructured covariance matrix will initially be used to model the covariance among repeated measures; however, if the model fails to converge using this covariance structure, either heterogeneous TOEPLITZ, homogeneous TOEPLITZ, or compound symmetry will be implemented according to the AICc.

6.5.7.6.3 Sensitivity Analyses for Other Pre-specified Efficacy Endpoints

For quantitative efficacy variables, two-sample t-tests, Wilcoxon rank sum tests and mixed-effect repeated measures analysis will be presented as sensitivity analyses.

For qualitative efficacy variables, Pearson chi-squared analysis comparing the treatment groups will be performed as sensitivity analyses.

Sample Pearson chi-squared analysis code:

```
PROC FREQ DATA=INDATA;
  TABLES <TREATMENT>*<ENDPOINT> / CHISQ;
RUN;
```

6.5.8 Statistical/Analytical Issues

6.5.8.1 Study Days

Study Day 1 will be defined as the date of Visit 1/Day 1. For events before the Day 1 visit, the study day will be calculated as the difference in day between the Day 1 visit and the date of interest. Thus, the day prior to the Day 1 visit will be defined as Day -1.

6.5.8.2 Analysis Visits

The eCRF nominal study visits will be used for analysis. For subjects who withdraw from the study, if they withdraw at a regular scheduled visit, the data collected at the time of withdrawal will be summarized under the regular visit; if they withdraw between scheduled visits, the early termination visit will be treated as an unscheduled visit. For the purposes of table summarization, the first visit for each nominal study visit will be used.

6.5.8.3 Study Baseline

Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment as documented in the subject dosing diary. Per the schedule of assessments in the protocol, this is expected to be the Visit 1 value. Measurements that are obtained after the first dose of randomized study treatment will be considered post-baseline values. If a measurement of a variable is not made on a given subject prior to the first dose of randomized study treatment, then that subject will be considered not to have a baseline value for that variable. CFB is defined as post-baseline assessment minus baseline assessment.

6.5.8.4 CDISC Standards

The exchange and terminology standards outlined in Section 4 will be used to create SDTM domains and ADaM datasets. A reviewer's guide and define.xml will be produced for each set. The ADaM datasets will be used to support all tables, listings, and figures with the exception of the pregnancy results listing which will be generated from SDTM. All data in the ADaM datasets will be used as the population for listings. At least one listing will be created for each ADaM dataset to display (a) most collected variables, and (b) derived variables used in the tables and figures. The source listing(s) will be referenced in all table and figure footnotes.

6.5.8.5 Adjustment for Covariates

The primary endpoints are CFB in total corneal fluorescein staining (NEI scale) at Day 57 and CFB of Dryness Score (VAS) at Day 57. The two primary endpoints will be analyzed separately using an ANCOVA model with baseline measurement as a numeric covariate and treatment as the main effect.

Subject randomization is stratified by clinical site and dryness score <70 vs ≥ 70 (VAS) at baseline (Visit 1). The analyses will not be adjusted for the stratification factors.

6.5.8.6 Handling of Dropouts or Missing Data

Missing data will be handled as follows. Missing data for other data points not covered below will be left as missing. Nominal visits for subjects who withdraw will be handled per Section 6.5.8.2.

6.5.8.6.1 Imputation Method for Efficacy Endpoints

The primary analysis will be completed on the FAS with available data per subject, assuming the overall study discontinuation rate is <5%. If the overall study discontinuation rate is ≥5% then the primary analysis will be based on the primary imputation methodology as defined Section 6.5.7.3 and the available data analyses will become robustness analyses.

Additionally, robustness analyses will include repeating the primary analysis on the per protocol set (PPS); the FAS imputing missing data using last observation carried forward (LOCF); the FAS imputing missing data using Markov Chain Monte Carlo (MCMC) multiple

imputation methodology under different assumptions of missingness (at random and not at random) each using 30 imputed values.

6.5.8.6.2 Missing Dates

All missing dates for medications or events that occur after randomization will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, missing months and days will be imputed as "01", provided this occurs on or after the date of first study drug self-administration. Otherwise, the date or month (as appropriate) of the first self-administration of study drug will be used

- For stop dates, missing months will be imputed as "12" and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used

The imputed dates will only be used to classify events, medications, or therapy as treatment emergent or concomitant. Imputed dates will only be used in the table analyses. Listings will display the available date data.

6.5.8.6.3 Adverse Events

Whether the adverse event occurred after the first dose of study drug, relationship, and severity should not be missing and will be queried for value. If missing data is present, the AE date will be imputed as detailed above, will be assumed to be related to study drug, and will be assumed to be severe.

6.5.8.7 Interim Analyses and Data Monitoring

No interim analyses are planned for this trial.

6.5.8.8 Multicenter Studies

No formal by site analyses will be conducted. Analyses by sites for sites with a sufficient number of subjects can be conducted in an adhoc manner to confirm the uniformity of the overall results.

6.5.8.9 Multiple Comparisons/Multiplicity

To control for inflation of type 1 error rate due to multiple hypotheses, the analysis of the two primary endpoints will be conducted in a hierarchical manner.

If both primary endpoints demonstrate statistically significant superiority of NOV03 versus saline at the two-sided alpha = 0.05 level, the following secondary endpoints will be tested hierarchically to maintain an overall two-sided alpha = 0.05.

1. CFB of Dryness Score (VAS) at Day 15
2. CFB in total Corneal Fluorescein Staining (tCFS) (NEI scale) at Day 15

3. CFB of VAS burning/stinging at Day 57
4. CFB in central Corneal Fluorescein Staining (cCFS) (NEI scale) at Day 57

6.5.8.10 Use of an "Efficacy Subset" of Subjects

The primary analysis will be repeated in the PPS with observed data only as sensitivity analysis. Subjects in the PPS will be analyzed as treated.

6.5.8.11 Examination of Subgroups

If imbalances of interest are noted in the demographics and baseline characteristics, ad hoc summaries by subgroup can be produced.

6.5.9 Safety Analyses

All safety analyses will be performed on the SAF. The primary evaluation of safety of the active arm will be against the control arm.

6.5.9.1 Adverse Events

6.5.9.1.1 General Considerations for Analysis of Adverse Events

General considerations for AE summaries and calculations are:

- Multiple events by PT and SOC will be counted once per subject for each treatment
- For summaries by severity, the most severe event will be selected
- For summaries by relationship, the most related event will be selected

6.5.9.1.2 Adverse Event Dictionary

AEs will be coded using MedDRA version 22.1 or higher. Tables and listings will present data at the system organ class and preferred term level.

6.5.9.1.3 Treatment-Emergent Adverse Events

A treatment emergent adverse event (TEAE) is an AE that occurs or worsens after the first dose of trial treatment.

Where an AE is associated with a partially or fully missing start date or time, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is treatment emergent.

6.5.9.1.4 Adverse Event Severity

All AEs will be categorized as mild, moderate, or severe as directed in the study protocol.

6.5.9.1.5 Relationship of Adverse Events to Study Drug

All AEs will be categorized as related or not related as determined by investigator using these explanations as specified in the study protocol:

- Suspected: A reasonable possibility exists that the investigational product caused the AE
- Not Suspected: A reasonable possibility does not exist that the investigational product caused the AE

6.5.9.1.6 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator, medical monitor or sponsor, it results in any of the following outcomes as specified in the protocol:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Medically important

6.5.9.1.7 Summaries of Adverse Event

Treatment-emergent AEs will be summarized. Number of subjects or eyes experiencing a TEAE will be summarized by SOC and PT by treatment group and overall. In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count based on the total column.

Summary tables (number and percentage of subjects) of AEs will be provided by treatment as follows:

- All treatment-emergent AEs by SOC
- All treatment-emergent AEs by SOC and PT
- All treatment-emergent AEs by SOC, PT and maximal severity
- All treatment-emergent AEs by SOC, PT and strongest relationship
- All treatment-emergent AEs by SOC, PT, maximal severity, and strongest relationship
- All serious treatment-emergent AEs by SOC and PT
- All treatment-emergent AEs leading to premature discontinuation of treatment by SOC and PT
- All non-serious treatment-emergent AEs by SOC and PT occurring at the PT level at rates of 1%, 2%, 3%, 4%, and 5% in at least one treatment arm, separately by percentage

Separate summaries will be performed for ocular and non-ocular AEs. Ocular AEs will be summarized at the subject and eye levels, with separate eye level summaries for study and fellow eye.

An overview table will be provided summarizing the number of:

- TEAEs
- Serious TEAEs
- Serious TEAEs by reason for seriousness
- TEAEs leading to premature discontinuation of treatment
- TEAEs by worst severity
- TEAEs by worst relationship
- TEAEs by pattern
- TEAEs by outcome
- TEAEs by action taken
- TEAEs by action taken related to investigational product
- TEAEs in the investigator's opinion that are ongoing and should be recorded as medical history of the NVU-004 study, and TEAEs by body system.

The treatment groups will be compared in regard to safety endpoints descriptively. No inferential comparison will be conducted.

6.5.9.2 Safety Laboratory Values

Safety laboratory tests will not be collected. Urine pregnancy test results will be captured at Visit 0, Visit 1, and Visit 4. Urine pregnancy test results will be included in a listing.

6.5.9.3 Vital Sign Measurements

Vital signs data will not be collected.

6.5.9.4 Other Safety Measurements

Visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics in SAF. Changes from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

6.5.9.4.1 Visual Acuity

Visual acuity will be performed at screening, Visits 1-4, and early termination. The base logMAR, which is the last line in which a letter is read correctly, and the number of total letter missed up to and including the last line read will be collected on the CRF. The calculated logMAR will be automatically generated by the EDC as base logMAR + (number of total letters missed × 0.02). Descriptive statistics for the calculated LogMAR Score will be presented for study eye and fellow eye by treatment and overall at baseline and all post-baseline visits in the SAF. Changes from baseline will also be summarized.

6.5.9.4.2 Slit-lamp Biomicroscopy

Biomicroscopy will be performed at screening, Visits 1-4, and early termination. Observations will be graded as Normal, Abnormal Clinically Significant, or Abnormal Not Clinically Significant . Lids, cornea, conjunctiva, anterior chamber, iris and lens will be

examined. If 'Check if no changes since Visit 0' is checked, the results of the tests at Visit 0 will be used for analysis at that timepoint. Listings will display 'No changes since Visit 0'. Descriptive statistics for the grading by each domain will be presented for study eye and fellow eye by treatment and overall at baseline and all post-baseline visits in the SAF. Shifts from baseline indicative of worsening will also be summarized. Worsening is defined as a shift from normal to abnormal not clinically significant, normal to abnormal clinically significant, and abnormal not clinically significant to abnormal clinically significant.

6.5.9.4.3 Dilated Fundoscopy Examination

A dilated fundoscopy examination will be performed during the trial at screening, Visit 4 and early termination. Observations will be graded as Normal, Abnormal CS or Abnormal NCS. Vitreous, retina, macula, choroid and optic nerve will be examined. If 'Check if no changes since Visit 0' is checked, the results of the tests at Visit 0 will be used for analysis at that timepoint. Listings will display 'No changes since Visit 0'. Descriptive statistics for the grading by each domain will be presented for study eye and fellow eye by treatment and overall at baseline and all post-baseline visits in the SAF. Shifts from baseline indicative of worsening will also be summarized. Worsening is defined as a shift from normal to abnormal not clinically significant, normal to abnormal clinically significant, and abnormal not clinically significant to abnormal clinically significant.

6.5.9.4.4 Intraocular Pressure

Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg at screening, Visit 4 and early termination. A single measurement will be made to obtain a determination of IOP. Descriptive statistics for the IOP measurement will be presented for study eye and fellow eye by treatment and overall at baseline and all post-baseline visits in the SAF. Changes from baseline will also be summarized.

6.5.10 Determination of Sample Size

The statistical hypotheses for the primary endpoint of CFB corneal fluorescein staining (NEI scale) total score at Day 57 are as follows:

H_{01}: The difference, between study eyes treated with NOV03and study eyes treated with saline, in the mean CFB corneal fluorescein staining (NEI scale) total score at Day 57 = 0.

H_{A1}: The difference, between study eyes treated with NOV03 and study eyes treated with saline, in the mean CFB corneal fluorescein staining (NEI scale) total score at Day 57 $\neq$ 0, with superiority claimed if the difference is less than 0 (NOV03 minus saline).

The statistical hypotheses for the hierarchical primary endpoint of the CFB Dryness Score at Day 57 are as follows:

H_{02}: The difference, between subjects treated with NOV03 and subjects treated with saline, in the mean CFB Dryness Score at Day 57= 0.

H_{A2}: The difference, between subjects treated with NOV03 and subjects treated with saline, in the mean CFB Dryness Score at Day 57 $\neq$ 0, with superiority claimed if the difference is less than 0 (NOV03 minus saline).

Two hundred fifty (250) subjects (study eyes) per treatment group yields 97.9% power to reject H_{01} in favor of HA1 and conclude superiority of NOV03 over saline in the mean CFB tCFS score at Day 57 assuming a true difference (NOV03 minus saline) of -1.0, a common standard deviation of 2.8, and a two-sided alpha = 0.05. Two hundred fifty (250) subjects per treatment group yields 97.9% power to reject H_{02} in favor of H_{A2} and conclude superiority of NOV03 over saline in the mean CFB Dryness Score (VAS) at Day 57 assuming a true difference (NOV03 minus saline) of -10, a common standard deviation of 28, and a two-sided alpha = 0.05. Accounting for an assumed 10% subject discontinuation rate, approximately 560 subjects (280 subject each arm) will be randomly assigned to trial treatment such that approximately 250 evaluable participants per arm complete the trial.

Therefore, assuming independence between tCFS score and Dryness Score (VAS), 250 FAS subjects per treatment group at Day 57 yields 97.9%* 97.9%= 95.8% power to reject both H_{01} and H_{02}. A positive correlation between these two endpoints would increase the overall power.

6.6 Changes in Planned Analyses

None.

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8 REFERENCES

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