Clinical Trial Protocol

Protocol 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 (Mojave Study)
Protocol Number:	904
Trial Phase:	3
Investigational Product Name:	NOV03 (100% perfluorohexyloctane)
IND Number:	IND 130558
Indication:	Dry Eye Disease (*keratoconjunctivitis sicca*) [redacted]
Investigators:	Multi-Center
Sponsor:	Bausch & Lomb, Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807 USA
Clinical Research Organisation:	[redacted]
IRB/IEC:	Sterling IRB [redacted]
Version:	2.0
Original Protocol Date:	05 AUG 2020
Amendment 1 Date	09 NOV 2020

Confidentiality Statement

This protocol contains confidential, proprietary information of Bausch & Lomb, Inc. Further dissemination, distribution or copying of this protocol or its contents is strictly prohibited.

Regulatory Statement

This trial will be performed in compliance with the protocol and in accordance with Good Clinical Practice (International Conference on Harmonisation [ICH], Guidance E6), principles of human subject protection, and applicable country-specific regulatory requirements.

1 SYNOPSIS AND TRIAL CONTACT INFORMATION

1.1 TRIAL CONTACT INFORMATION

SPONSOR PERSONNEL

[redacted]	[redacted]
[redacted]	[redacted]

MEDICAL MONITOR

[redacted]

Clinical Research Organization (CRO) PERSONNEL

[redacted]	
[redacted]	[redacted]

1.2 SYNOPSIS

Protocol 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 (Mojave Study)
Protocol Number:	904
Investigational Medicinal Product:	NOV03 (100% perfluorohexyloctane)
Control:	Saline solution: 0.6% sodium chloride solution
Trial Phase:	3

Trial Objective:	The objectives of this trial are to assess the efficacy, safety, and tolerability of NOV03 ophthalmic solution in comparison to a saline control for the treatment of the signs and symptoms of Dry Eye Disease (DED) [redacted]
Overall Trial Design	
Structure:	Multi-center, randomized, double-masked, saline-controlled
Participant Duration:	An individual subject's participation is estimated to be approximately 10 weeks.
Trial Duration:	The estimated trial duration is approximately 7 months, from first subject first visit to last subject last visit.
Dosage/Dose Regimen:	Subjects eligible for randomization will receive one of the following treatments to be administered bilaterally from Visit 1 to Visit 4. 1) NOV03 (100% perfluorohexyloctane) 4 times daily (QID) 2) Saline solution (0.6% sodium chloride solution) 4 times daily (QID)
Summary of Visit Schedule:	5 visits over the course of approximately 10 weeks • Visit 0 = Screening within 14 days before Visit 1 (Day -14 to -1) • Visit 1 = Day 1, Baseline/Randomization • Visit 2 = Day 15 ± 1 days, • Visit 3 = Day 29 ± 2 days • Visit 4 = Day 57 ± 2 days
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double-masked, multi-center trial. Subjects will be instructed not to show or discuss the properties of the assigned Investigational Medicinal Product (IMP) and/or their experience with the IMP with other trial participants, and not to show or discuss the IMP with the Investigator or site staff other than the dedicated dosing coordinator, unless instructed to do so. A dedicated dosing coordinator at each site will be responsible for instructing subjects regarding IMP handling/administration, IMP dispensation and accountability, reviewing daily dosing diaries, performing the instillation comfort questionnaire, the Eyedrop acceptability questionnaire and all discussions with study subjects related to IMP.

Trial Population Characteristics	
Number of Subjects:	Approximately 760 subjects will be screened to enroll at least 560 subjects (280 each arm) at approximately 35 clinical sites.
Condition/Disease:	Dry Eye Disease (*keratoconjunctivitis sicca*) associated with Meibomian Gland Dysfunction
Inclusion Criteria:	**Subjects must:** 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 Tear film break-up time (TFBUT) ≤5 sec at Visit 0 and Visit 1. 5. Have Ocular Surface Disease Index (OSDI©) ≥25 at Visit 0 and Visit 1. 6. Have an unanesthetized Schirmer's Test I ≥5 mm at Visit 0 and Visit 1. 7. Have Meibomian Gland Dysfunction (MGD) defined as total MGD score ≥ 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 ≤ X ≤11 (i.e. sum of inferior, superior, central, nasal, and temporal) according to the National Eye Institute (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.
Exclusion Criteria:	**Subjects must not:** 1. Have been randomized in NVU-002, NVU-003, or participated in the NVU-004 OLE Study. 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 or anterior membrane dystrophy.

	3. Have a history of Stevens 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 likely require such treatment during the trial. Any other lid margin therapy such as lid scrubs, lid wipes, warm compresses, systemic antibiotics (such as tetracyclines) and oral supplements for treatment of ocular conditions 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, Intense Pulse Light (IPL) 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 (e.g. Botox injections for blepharospasm). 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 active ocular or systemic infection (bacterial, viral, or fungal), including fever requiring 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 study 904 or NVU-003 subject, or a family member living in the same household of another NVU-004 OLE participant. 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 a 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 ocular 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 corrected visual acuity worse than or equal to logarithm of the minimum angle of resolution (logMAR), +0.7 as assessed with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts 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. 31. Have a history of isotretinoin (e.g. Accutane, Myorisan, Claravis, Amnesteem) use.
Trial Formulations:	• 100% Perfluorohexyloctane • Saline Solution (0.6% sodium chloride solution)
<u>Evaluation Criteria</u>	
Efficacy Endpoint(s):	**Primary Efficacy Endpoints:** The following primary endpoints will be tested using a hierarchical fixed sequence testing to maintain an overall two-sided alpha = 0.05 level: 1. Change from baseline (CFB) in total Corneal Fluorescein Staining (tCFS) (NEI scale) at Day 57 2. CFB of Dryness Score (visual analogue scale [VAS] Severity of Dryness) at Day 57 **Secondary Efficacy Endpoints:**

	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 **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 Ocular Surface Disease Index (OSDI©) at each measured post-baseline visit. [redacted]
Safety Endpoints:	1. Ocular and non-ocular Treatment Emergent Adverse Events (TEAEs) 2. Visual Acuity 3. Slit-Lamp Biomicroscopy 4. Intraocular Pressure 5. Dilated Fundoscopy
[redacted]	[redacted]
General Statistical Methods and Types of Analyses	

The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

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 NOV03 and 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 ≠ 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 (VAS) 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 (VAS) at Day 57= 0.

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

The study has been designed to have 95% power to reject both H_{01} and H_{02} assuming independence between the sign and symptom endpoint; positive correlation between these two endpoints would increase the overall power.

Estimated mean differences (common standard deviations) in CFB to Day 57 using an ANCOVA analysis with CFB to Day 57 as the response, baseline as a covariate and treatment as the fixed effect from NVU-002 are: -1.2 (2.5) for tCFS and -11 (26) for Dryness Score. Conservative estimates of -1.0 (2.8) for tCFS and -10 (28) for Dryness Score are used for sample size calculation.

Two hundred fifty (250) subjects (study eyes) per treatment group yields 97.9% power to reject H_{01} in favor of H_{A1} 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}.

Hierarchical fixed sequence testing will be employed to maintain the type I error rate. The primary analyses will first test the difference in the mean CFB corneal fluorescein staining (NEI scale) total score between treatments at Day 57. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of NOV03 then the trial will be considered a success; NOV03 will be declared to be superior to saline in the mean CFB corneal fluorescein staining (NEI scale) total score at Day 57; and the difference in the mean CFB total Dryness Score between treatments at Day 57 will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean CFB corneal fluorescein staining (NEI scale) total score at Day 57 is in favor of NOV03, and the test of the difference in the mean change from Dryness Score at Day 57 is also statistically significant in favor of NOV03, then NOV03 will be declared to be superior to saline in both the mean CFB corneal fluorescein staining (NEI scale) total score and the mean CFB of the Dryness Score at Day 57.

If both primary endpoints demonstrate statistically significant superiority of NOV03 versus saline at the two-sided alpha = 0.05 level, a hierarchical testing of the secondary endpoints will be performed.

Primary Efficacy Analyses:
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 [VAS]) will be 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.
Two-sample t-tests, Wilcoxon rank sum tests and mixed-effect repeated measures analysis comparing treatment groups will be performed as sensitivity analyses.
The primary analysis of the primary endpoints will use the Full Analysis Set (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 primary imputation methodology as detailed in the statistical analysis section and the available data analyses will become robustness analyses.

Additional 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.

Further Efficacy Analyses:
The following secondary endpoints will be tested hierarchically:

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

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.

The primary analysis of the secondary endpoints will use the Full Analysis Set (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 follow the same imputation strategy detailed for the primary endpoints.

Quantitative secondary and other pre-specified efficacy endpoints 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 and CFB. 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.

Two-sample t-tests, Wilcoxon rank sum tests and mixed-effect repeated measures analysis will also be presented as sensitivity analyses. The other pre-specified analyses will use the Full Analysis Set (FAS) with available data per subject.

Other pre-specified 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. Pearson chi-squared analysis comparing the treatment groups will be performed as sensitivity analyses.

Safety Variables:
Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment

group. An AE is treatment emergent if it occurs or worsens after the first dose of trial treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class, preferred term and strongest relationship; and by system organ class, preferred term, maximal severity, and strongest relationship. Separate summaries will be performed for ocular and non-ocular TEAEs. Other safety endpoints including assessments of visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BCVA	Best-corrected Visual Acuity
BID	Two times daily
BOCF	Baseline Observation Carried Forward
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
cCFS	Central Corneal Fluorescein Staining
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
eCRF	electronic Case Report Form
EDC	Electronic Data Capturing system
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional/Independent Review Board
IPL	Intense Pulse Light
IUD	Intra-Uterine Device
IRS	Interactive Response System
logMAR	logarithm of the Minimum Angle of Resolution
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
NEI	National Eye Institute
NOV03	100% perfluorohexyloctane
OD	right eye
OS	left eye
OSDI©	Ocular Surface Disease Index

PPS	Per Protocol Set
QID	Four times a day
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SMP	Safety Management Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment-emergent Adverse Events
tCFS	total Corneal Fluorescein Staining
TFBUT	Tear Film Break-up Time
VA	Visual Acuity
VAS	Visual Analog Scale

2 INTRODUCTION

2.1 Dry Eye Disease (DED)

Dry Eye Disease (DED) is defined by the International Dry Eye Workshop (DEWS) as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig et al., 2017). Symptoms of DED such as feeling of dryness, burning, a sandy/gritty sensation, foreign body sensation, pain or itchiness are quite debilitating. In addition, visual function related symptoms such as fluctuating vision with blinking, blurred vision, and difficulty with reading despite perfect visual acuity is an important and underestimated aspect of the disease. In consequence, DED negatively impacts quality of life comparably to other severe diseases (Schiffman et al., 2003), and adverse effects on mental health, such as depression and anxiety, have been observed (Le et al., 2012). DED is a serious and chronic disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to permanent vision loss due to corneal complications (Lemp et al., 1995).

As many as 5 - 35% of subjects visiting ophthalmic clinics report dry eye symptoms, making it one of the most common conditions seen by ophthalmic specialists (McCarty et al., 1998; Lin et al., 2003). Estimates of the prevalence of dry eye vary considerably, depending on the criteria used to define the disease, but in the United States (US), it has been estimated that as many as 3.2 million women and 1.7 million men over the age of 50 have DED, with a projected 40% increase in the number of patients affected by 2030 (Schaumberg et al., 2002; Schaumberg et al., 2003; Schaumberg et al., 2009) With the aging population in the US and other countries of the developed world, and with increasing computer use, DED is expected to continue to become more prevalent and finding a treatment is becoming more important (Benitez-del-Castillo et al., 2017).

2.2 Product Rationale

NOV03 is a sterile ophthalmic eye drop formulation, developed for the treatment of the signs and symptoms of DED [redacted]

It is a single component product consisting of 100% perfluorohexyloctane. NOV03 addresses DED associated with MGD via a new physicochemical mode of action. Due to its low surface tension it rapidly spreads across the ocular surface and interacts with the lipophilic part of the tear film forming a layer at the tear film air interface. Such a layer prevents excessive evaporation of the aqueous tear film component. [redacted]. As a water-free, single component product, it is free of excipients like oils, surfactants and preservatives. Related advantages include convenient handling, improved tolerability, and a decrease in the visual disturbance upon instillations.

Due to this mode of action subjects with DED associated with MGD were considered to experience the greatest benefit from the treatment. This is in line with experience from the

[redacted]

For the US development of NOV03, the phase 2 clinical trial NVU-002 (SEECASE-1) was conducted in US clinical sites. NVU-002 was designed to specifically include a DED population with an MGD component. In NVU-002, subjects improved clinically significantly from treatment with NOV03. The magnitude of symptom improvement was large (in the 50% range) for many of the VAS items in the NOV03 groups.

2.3 Trial Rationale

[redacted]

2.4 Summary of Known and Potential Risks and Benefits to Human Subjects

The active and only ingredient of NOV03, perfluorohexyloctane, is a semifluorinated alkane with a well-established tolerability and safety profile. [redacted] It is not yet approved in the US.

Safety data from the NVU-002 trial showed an excellent clinical safety and tolerability profile. No remarkable imbalance in terms of treatment emergent adverse events (TEAEs) across treatment groups were revealed. Incidence of ocular AEs was low, ranging from 4.5% to 11.7%, and the great majority were of mild intensity. Instillation site reactions were reported in single cases in 3 (2.6%) subjects in NOV03 QID, 1 (0.9%) subject in NOV03 BID and 2 (1.8%) subjects in the saline group. A total of 4 serious adverse events (SAEs) were reported in 4 subjects. Three (3) subjects were randomized to the NOV03 QID group and 1 subject was randomized to the NOV03 BID group. All SAEs were non-ocular and not related to trial treatment. All SAEs resolved.

Slit-lamp biomicroscopy, dilated fundoscopy, mean best corrected visual acuity (BCVA) and intraocular pressure (IOP) observations did not indicate any treatment-related changes. There were no clinically significant changes in vital signs, laboratory parameters or other observations related to safety.

Up to now four AEs of blurred vision have been reported, two were assessed as not related and two as related. If any visual disturbances should occur upon instillation of the drop the subject is advised not to drive or use machines until such effects have disappeared.

[redacted]

As described in Section 2.3 the NVU-002 trial demonstrated a favorable efficacy in reducing signs and symptoms of DED in subjects with evaporative forms of DED [redacted]. This efficacy profile is supported by experience from the Post Market Clinical Follow-up studies.

In summary, based on the preclinical and clinical data obtained to date, risks to subjects in the planned NVU-003 trial are considered very low. Furthermore, the subjects randomized in this trial will be closely monitored, and current standard ophthalmological safety assessments will be performed during the entire treatment period.

The efficacy demonstrated to date shows that NOV03 reduces DED signs as well as DED symptoms stronger than the saline comparator in the target population of subjects with DED [redacted]

NOV03 therefore provides a favorable benefit-risk treatment profile to subjects with DED [redacted] The study 904 trial is designed to replicate the results of the NVU-003 study and confirm the positive benefit-risk profile.

3 TRIAL OBJECTIVES

3.1 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 Dry Eye Disease associated with MGD.

3.2 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 Dry Eye Disease associated with MGD.

- 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 Dry Eye Disease associated with MGD.

4 TRIAL DESIGN

4.1 Overall Trial Design

This trial 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 comprised of 280 subjects such that approximately 250 evaluable subjects per arm complete the trial. Approximately 35 clinical sites are anticipated to participate.

This trial will consist of two periods: Up to 14-day screening period and a 57-day treatment period (See Appendix 1).

4.2 End of Trial Definition

The end of the trial for an individual subject is defined as that subject's last clinic visit or the date of early termination, if applicable. For subjects that are lost to follow-up, the date of early termination will be the date of the last attended clinic visit. The end of the trial for the overall trial is defined as completion of the last visit or procedure as specified in schedule of assessments for all subjects in the trial.

4.3 Visit Description

Subjects will be required to sign an Informed Consent before completing any trial related procedures. All trial procedures are listed in Section 8.4 and in the schedule of assessments (see Appendix 1). The ocular symptoms assessments and evaluations must be performed in the respective order as listed. IMP Dispensation is described in Section 7.1.4.

Subjects will be instructed not to show or discuss the properties of the assigned IMP and/or their experience with the IMP with other trial participants, and not to show or discuss the IMP with the Investigator or site staff other than the dedicated dosing coordinator, unless instructed to do so.

Screening (Visit 0)

All assessments required for the screening visit must be done within 14 days before the randomization, baseline Visit 1. At least one eye must qualify with all of the following objective measures: Tear film break up time ≤5 sec, Schirmer's Test ≥5 mm, Meibomian gland dysfunction (MGD) defined as MGD score ≥ 3, and total Corneal Fluorescein Staining (CFS) of $4 \leq x \leq 11$. Subjects who fail to qualify for the trial at screening may be rescreened as described in Section 5.5.

Baseline Day 1 (Visit 1)

On Day 1 (Visit 1), eligible subjects will be evaluated for baseline signs and symptoms of dry eye disease and will be randomized to NOV03 QID or saline solution QID. Subjects will be given a 14-day supply and will self-administer a single drop of the first initial trial medication into each eye at the clinic. Subsequently the subject will be asked to complete an instillation comfort questionnaire. Each subject will be given a dosing diary to record

dosing. Study staff will help the subject to understand how to use the dosing diary and when the remaining doses should be taken.

Visits 2-4 / (ET)

Subjects will return to the clinic on Day 15±1 (Visit 2), 29±2 (Visit 3), and 57±2 (Visit 4/Early Termination (ET)) to be evaluated for signs and symptoms of dry eye disease. The subject will be asked to complete an eyedrop acceptability questionnaire during Visit 4. Collection and review of IMP will be performed (used and unused trial medication should be returned to the clinic) and new trial medication will be dispensed at Visit 2 and Visit 3. The dosing diary will be collected at the clinic during each visit and checked for compliance. Subjects will be discharged from the trial after all Visit 4/ET assessments have been completed.

Early Termination

Subjects who terminate early during the treatment period will be asked to complete all assessments as indicated at Visit 4 on the schedule of assessments prior to commencement of any alternative dry eye therapy (if considered possible). Subjects who are terminated early from the trial will not be replaced.

Trial Flow

All subjects will be expected to progress from screening through trial exit. All subjects will follow the trial structure as shown in Figure 1.

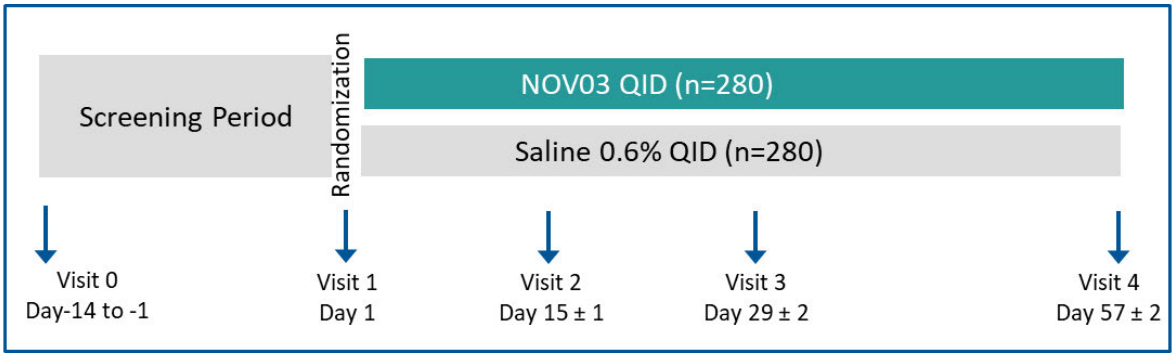

Figure 1 Study 904 Flow Chart

4.4 Enrollment and Treatment Assignment

All treatment groups will be enrolled in parallel. Each subject will be assigned a unique subject number. All subject numbers will be assigned by Interactive Response System (IRS) in strict numerical sequence and no numbers will be skipped or omitted. If all eligibility criteria are met at Visits 0 and 1, each qualifying subject will then be randomized.

Site and Dryness Score <70 vs ≥ 70 (VAS) at baseline (Visit 1) are used as a stratification factor in this trial. IRS will be used to account for the stratification factors while assigning the drug kit numbers at visits 1, 2 and 3. The subjects, investigators, Clinical Research Organization (CRO) personnel involved in conduct and monitoring of the trial and sponsor will be masked to IMP assignment.

Each subject will participate in the trial for approximately 10 weeks. The total duration of the trial from First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV) is expected to be approximately 7 months.

4.5 Justification of Trial Design

This trial is designed as a confirmatory trial to the previously conducted phase 2 trial NVU-002 and a supportive trial to the ongoing phase 3 trial NVU-003 in subjects with DED associated with MGD. This population is considered to respond best based on the mode of action and clinical data.

The trial will be a randomized, double-masked, saline controlled trial to demonstrate efficacy and safety of NOV03 after a 2-month treatment duration. Vehicle controlled trials are currently the standard for DED trials, however, as NOV03 is a 100% single component product, saline solution has been selected as comparator given that this most likely best reflects a placebo treatment. Randomization and double masking are state of the art measures to reduce bias. Fast onset of efficacy is important for subjects and their compliance to therapies, thus early demonstration of efficacy (e.g. at 2 month) is desired and highly clinically relevant. Moreover, DED is a fluctuating condition with recurring dry eye complaints that may be linked to seasonal and/ or environmental changes (Van Setten et al., 2016), thus a primary endpoint assessment following a shorter treatment duration is considered clinically relevant and has a greater potential to capture the true drug effect.

[redacted]

The two primary endpoints, tCFS and Dryness Score, will be tested in a hierarchical order with total corneal fluorescein staining being tested first as the NVU-002 data for this endpoint is stronger. The hierarchical testing has been selected to protect the α – error.

4.6 Justification of Dose

The NOV03 QID dosing regimen to be evaluated in this trial is based on the results from the phase 2 NVU-002 trial. The QID regimen showed more pronounced reductions in tCFS and symptom scores as measured by OSDI and VAS. This was confirmed by responder analyses on signs (tCFS) as well as symptoms (Dryness Score) that underlined the relevance of these observed changes.

Based on the safety and tolerability profile seen for both treatment regimens in NVU-002 and the consistent trend for better efficacy in NOV03 QID in both signs and symptoms the QID dose regimen will be tested in this trial. The aim of the current trial study 904 is to replicate the efficacy and safety results of NVU-002 and to provide additional supportive data in addition to the phase 3 trial NVU-003.

5 TRIAL POPULATION

5.1 Number of Subjects (approximate)

An estimated 760 subjects will be screened to randomly assign at least 560 subjects to IMP such that approximately 250 evaluable subjects per treatment arm complete the trial.

5.2 Trial population characteristics

All subjects must be at least 18 years of age, of either gender and 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.

5.3 Inclusion Criteria

Subjects will be eligible to participate in this trial if they **meet all** following 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 Tear film break-up time (TFBUT) ≤5 sec at Visit 0 and Visit 1.
5. Have Ocular Surface Disease Index (OSDI©) ≥25 at Visit 0 and Visit 1.
6. Have an unanesthetized Schirmer's Test I ≥5 mm at Visit 0 and Visit 1.
7. Have Meibomian Gland Dysfunction (MGD) defined as total MGD score ≥ 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≤ X ≤11 (i.e. sum of inferior, superior, central, nasal, and temporal) according to the National Eye Institute (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.

5.4 Exclusion Criteria

Subjects will not be eligible to participate in this trial **if any** of the following criteria apply**:**

1. Have been randomized in NVU-002, NVU-003 or participated in the NVU-004 OLE Study.
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, history of eye trauma or anterior membrane dystrophy.
3. Have a history of Stevens 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 (such as tetracyclines) 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, Intense Pulse Light (IPL) 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 (e.g. Botox injections for blepharospasm).
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 active ocular or systemic infection (bacterial, viral, or fungal), including fever requiring 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 study 904 or NVU-003 subject, or a family member living in the same household of another NVU-004 OLE participant.
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 ocular 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.
31. Have a history of isotretinoin (e.g. Accutane, Myorisan, Claravis, Amnesteem) use.

5.5 Re-Screen Procedures

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 is signed, new subject number is received via IRS and all the assessments are repeated as per protocol requirements.

5.6 Subject/Trial Withdrawal Criteria

Subjects are free to discontinue their participation in the trial at any time without giving their reasons.

A subject **must be** discontinued after randomization **from the trial** for any of the following reasons:

- Occurrence of pregnancy;
- Withdrawal of subject`s consent;
- Emergency unblinding has occurred.

A subject **must be** discontinued **from treatment** after randomization for any of the following reasons (but may remain in the trial for follow up assessments):

- If at any time during the trial the investigator determines that a subject's safety has been compromised;
- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety;
- If discontinuation is considered necessary by the investigator and/or sponsor;
- Occurrence of Adverse Events (AEs) that present an unacceptable consequence or risk to the subject in the judgment of the investigator, sponsor, or the medical monitor; or is intolerable to the subject.

If a subject has failed to attend scheduled trial assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case a subject has to be withdrawn from the trial for safety reasons related to study drug, the sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned or the subject´s health has reached a stable condition.

Subjects who are withdrawn from the trial after dosing will not be replaced.

In case of premature withdrawal from the trial, the process outlined in Section 8.4.2 should be followed. In any case, the appropriate electronic Case Report Form (eCRF) section including the reason for discontinuation as defined in Section 8.6.2 must be completed.

The trial **can be** prematurely discontinued as described in Section 8.7.

6 TRIAL PARAMETERS

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoints:

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

1. Change from baseline (CFB) in total Corneal Fluorescein Staining (tCFS) (NEI scale) at Day 57
2. CFB of Dryness Score (visual analogue scale [VAS] Severity of Dryness) at Day 57

6.1.2 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 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

6.1.3 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 Ocular Surface Disease Index (OSDI©) at each measured post-baseline visit.

[redacted]

[redacted]

6.2 Safety Endpoints

1. Ocular and non-ocular TEAEs
2. Visual acuity
3. Slit-Lamp biomicroscopy
4. Intraocular pressure
5. Dilated fundoscopy

[redacted]

[redacted]

- [redacted]
- [redacted]

7 TRIAL MATERIALS

7.1 Investigational Medicinal Product(s)

7.1.1 IMP(s)/ Formulation (s)

NOV03 drug product is a thin, clear, preservative-free ophthalmic solution drop (see Table 1). Saline eye drops preserved with benzalkonium chloride will be supplied as the control product (see Table 2). Investigational drug and control will be provided in identical bottles and labels to ensure the double-masked character of the trial.

Table 1 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
[redacted]	[redacted]

Table 2 Control Investigational Product

	Control 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
[redacted]	[redacted]

7.1.2 Labeling and Packaging of IMP

IMP will be labelled according to the legal requirements and packaged into individual subject kits, each containing 2 bottles of NOV03 or saline solution. See Section 7.1.4 for details regarding dispensation to subjects.

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

7.1.3 IMP Storage

The IMPs must be stored in a secure area accessible only to the investigator or pharmacist and his/her designees. IMPs must be stored **at room temperature** under temperature-monitored conditions and must not be refrigerated. Subjects should be instructed to store IMP at room temperature and out of children's reach at home. Subjects should not use a dispensed bottle that has been opened for more than 30 days.

7.1.4 IMP Dispensation

- The dedicated dosing coordinator is responsible for dispensing the IMP and supervision of 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.
- At Visits 2, 3 and 4 used/unused IMP will be collected from subjects for drug accountability by the dedicated dosing coordinator.

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 subject 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.

7.1.5 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. Subjects will self-administer NOV03 or saline eye

drops in each lower cul-de-sac of each eye as shown in Appendix 2 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 for the duration of the trial. Clinic staff will coach the subjects to dose themselves at approximately the same time every day e.g., morning, lunch time/mid-day, afternoon/early evening, and at bedtime. If a dose is missed, then the next dose should be administered on time.
The dedicated dosing coordinator will inform subjects on how to store IMP (see Section 7.1.3) and dose IMP and how to complete their dosing diary.

Dosing should be continued until the day 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 dosing in their dosing diary. 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.

7.2 IMP Accountability

The dedicated dosing coordinator at each site must keep an accurate accounting of IMPs received from the supplier by maintaining a detailed inventory. IMP shipment records will be verified and accountability performed by comparing the IMP shipment inventory sheet to the actual quantity of used/unused IMP bottles received at the site.

Accurate records of receipt and disposition of the IMP (e.g. dates, quantity, subject number, kits used, kits unused, etc.) must be maintained by the dedicated dosing coordinator at each site. This includes the amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the sponsor or designee upon completion of the trial.

Investigational trial medication orders, records of receipts, dispensing records, and inventory forms will be examined and reconciled by the dedicated dosing coordinator. At each visit, subjects will return all bottles to clinic staff for accountability purposes. Accountability will be ascertained by performing reconciliation between the amount of IMP cartons (kits and their components) sent to the site, the amount used and unused at the time of reconciliation. All investigational trial medication that is dispensed during the course of the trial must be accounted for on an IMP accountability form. No IMP kits or bottles will be returned to the sponsor prior to full accountability by sponsor's monitor.

7.3 IMP Handling and Return

Unless otherwise directed, at the end of the trial all returned (used and unused) IMP must be directly shipped from the clinical site to the sponsor for destruction of the medications. **Note: The medications should not be disposed or returned prior to full accountability by the sponsor's monitor.** The clinical site will include a copy of all completed drug disposition forms with the IMP to the sponsor after full accountability is completed.

7.4 IMP Masking

Investigational drug and control will be provided in identical bottles and labels to ensure the double-masked character of the trial. The Investigator/site staff and Bausch & Lomb, Incorporated. personnel or designee(s) involved in the conduct of the trial will be masked to the IMP. Clinical Trial Material Supply Chain are unmasked designee.

Due to 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, accountability) surrounding the use of IMP.

Each site must have a dedicated dosing coordinator that will be responsible for:

- all IMP dispensation and accountability,
- daily diary dosing education/review,
- all discussions with study subjects related to IMP,
- the administration of the Eyedrop Acceptability and Instillation Comfort Questionnaires.

This designee shall not participate in any other trial procedures and not report this information to other staff. Subjects will be instructed to administer the IMP out of the sight of the Investigator or site staff other than the dedicated dosing coordinator. Subjects are not to show or discuss the properties of the assigned IMP to the Investigator or site staff other than the dedicated dosing coordinator, unless instructed to do so.

7.5 Other Trial Supplies

Diaries, Questionnaires, Urine Pregnancy Tests, Meibomian Gland Evaluator stick, Schirmer's test strips, sodium fluorescein, will be provided to sites. Respective instructions are available in Appendix 3 and manual of operations.

8 TRIAL METHODS AND PROCEDURES

8.1 Concurrent Medications and Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken. Concurrent or previous medications are to be recorded for 60 days prior to Visit 0. Any physical therapies, or surgeries are to be documented for 6 months prior to Visit 0.

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator and in consultation with the medical monitor. If there is any question as to whether the medication may interfere, the investigator should contact the medical monitor or sponsor. Whenever possible, medications should be administered in dosages that remain constant throughout the study duration.

Physical therapies such as lid scrubs, lid wipes, warm compresses, systemic antibiotics (such as tetracyclines) and oral supplements for treatment of ocular conditions must be stable within the last 30 days prior to Visit 1 and should be maintained stable throughout the trial. Changes in those therapies or initiation of such therapies should be recorded on the subject's source document and corresponding eCRF.

8.2 Prohibited Medications

Disallowed medications and treatments are listed in the exclusion criteria (Section 5.4). All medications and treatments that were not allowed prior to trial are also not allowed during the trial in particular wearing of contact lenses, ocular surgery/ocular laser treatment of any kind, and no other dry eye treatments such as artificial tears, gels, or ointments or TrueTear™ device (Intranasal Tear Neurostimulator) shall be used within 24 hours prior to Visit 1 and throughout the course of the trial.

Specific prohibitions:

- Topical ocular steroid treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0 and during the trial.
- 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. Amitriptyline (e.g., Elavil) is only allowed as sleep aid and should not be used within 24 hours prior to any visit (see Section 8.1).
- History of isotretinoin use

Concurrent enrollment in another investigational drug or medical device trial is not permitted.

[redacted]

8.4 Examination Procedures

8.4.1 Procedures to be performed at each trial visit with regard to trial objective(s)

See Appendix 1 for a schedule of visits and measurements in recommended order. Appendix 3 describes the eye examinations. These should not be done earlier than 2 hours after IMP instillation. If possible the same investigator/coordinator should perform the assessments for an individual subject. Primary endpoint assessments at Baseline Visit 1 (Day 1) and Visit 4 (Day 57) should be done preferably on the same time of the day.

The dedicated dosing coordinator will perform tasks as described in Section 7.4.

Visit 0 (Up to 14 days before Visit 1): Screening

- Informed consent / HIPAA;
- Demographic data and medical / medication history;
- Review of inclusion / exclusion criteria;
- Urine pregnancy test;
- Ocular Surface Disease Index (OSDI©) questionnaire;
- Visual acuity (ETDRS);
- Slit-Lamp biomicroscopy;
- Tear Film Break-up Time (TFBUT);
- Fluorescein staining (NEI scale);
- Meibomian gland assessment (MGD score) (wait 5 min prior start of Schirmer`s test);
- Schirmer's test I (without anesthesia);
- Intraocular pressure;
- Dilated fundoscopy;
- Non-leading AE questioning (Adverse event query);
- Qualified subjects will be scheduled for Visit 1.

Visit 1 (Day 1): Baseline/Randomization

- Previous/Concomitant Medication;
- Review of inclusion / exclusion criteria;
- Urine pregnancy test;
- Dryness Score (VAS Severity of Dryness);
- VAS for burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms;
- Ocular Surface Disease Index (OSDI©) questionnaire;
- Visual acuity (ETDRS);
- Slit-Lamp biomicroscopy;
- Tear Film Break-up Time (TFBUT);
- Fluorescein staining (NEI scale);
- Meibomian gland assessment (MGD score) (wait 5 min before start of Schirmer`s test);
- Schirmer's test I (without anesthesia);
- Randomization;
- In-office dose of IMP;
- Instillation comfort questionnaire;
- Non-leading AE questioning (Adverse event query);
- Dispensation of dosing diary;
- Drug dispensation of one kit for self-administered dosing until Visit 2;
  - Subjects will be instructed on how to administer IMP;
  - Subjects will be instructed to dose with IMP on the day of their next visit at least 2 hours before the start of their visit (Visit 2);
  - Subjects will be instructed on how to complete the dosing diary.

Visit 2 (Day 15 ± 1), Visit 3 (Day 29 ± 2):

- At the beginning of the visit the subject will be asked about the time of last dose. Assessments should be performed at least 2 hours after last dose of IMP;
- Collection and review of IMP and dosing diary;
  - Calculate subject compliance with doses in the subject diary as described in Section 8.5 and re-educate subject as necessary.
- Concomitant medication update;
- Dryness Score (VAS Severity of Dryness);
- VAS for burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms;
- Ocular Surface Disease Index (OSDI©) questionnaire;
- Visual acuity (ETDRS);
- Slit-Lamp biomicroscopy;
- Fluorescein staining (NEI scale);
- Non-leading AE questioning (Adverse event query);
- Re-dispensation of dosing diary;

Visit 2 Drug dispensation of one kit for self-administered dosing until Visit 3;
- Subjects will be instructed on how to administer IMP;
- Subjects will be instructed to dose with IMP on the day of their next visit at least 2 hours before the start of their visit (Visit 3);
- Subjects will be instructed on how to complete the dosing diary.

Visit 3 Drug dispensation of two kits for self-administered dosing until Visit 4;
- Subjects will be instructed on how to administer IMP;
- Subjects will be instructed to dose with IMP on the day of their next visit at least 2 hours before the start of their visit (Visit 4);
- Subjects will be instructed on how to complete the dosing diary.

Visit 4 (Day 57 ± 2) or ET:
- At the beginning of the visit the subject will be asked about the time of last dose. Assessments should be performed at least 2 hours after last dose of IMP;
- Collection and review of IMP and diary;
- Concomitant medication update;
- Urine pregnancy test;
- Dryness Score (VAS Severity of Dryness);
- VAS for burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms;
- Ocular Surface Disease Index (OSDI©) questionnaire;
- Eyedrop acceptability questionnaire;
- Visual acuity (ETDRS);
- Slit-lamp biomicroscopy;
- Tear Film Break-up Time (TFBUT);
- Fluorescein staining (NEI scale);
- Meibomian gland assessment (MGD score) (wait 5 min before start of Schirmer`s test);
- Schirmer's test I (without anesthesia);
- Intraocular pressure;
- Dilated fundoscopy;
- Non-leading AE questioning (Adverse event query);
- Trial exit.

8.4.2 Early Termination/Discontinuation

The following data from subjects discontinuing before randomization (i.e. screen failures) will be captured in the eCRF:
- Demographics
- AEs / SAEs
- Reason for discontinuation (including applicable assessment results)

If a randomized subject is discontinued from the trial prior to Visit 4 (Day 57 ± 2) and not willing to perform all subsequent visits and assessments, then all evaluations planned for

Visit 4 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

Randomized and dosed subjects who discontinue treatment for any reason will be encouraged to undergo all subsequent trial visits and assessments.

Data from subjects discontinuing after randomization will be captured completely in the eCRF including Early Termination Visit and reason for discontinuation.

8.4.3 Unscheduled Visits

An unscheduled visit may be performed during the course of the trial in order to ensure subject safety and/or to dispense additional IMP if necessary (i.e. damaged/lost or subject ran out of IMP in between visits). All procedures performed at an unscheduled visit will be recorded in the source documents and on the unscheduled visit eCRF pages. Any unscheduled visit procedure listed in the eCRF that is not performed should be indicated as "not done."

Evaluations that may be conducted at an unscheduled visit include:

- Slit-Lamp biomicroscopy;
- Visual acuity;
- Intraocular pressure;
- Dilated fundoscopy;
- Urine pregnancy test (for women of childbearing potential);
- Assessment of AEs;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of IMP at Visits 1, 2, and 3, and provided with written instructions (see Appendix 2). The used and unused IMP bottles will be collected from subjects at Visits 2, 3 and 4 to assess subject dosing compliance.

Subject dosing compliance will be determined by the subject's response or lack thereof to the prompt "Was the dose taken?" in the subject diary. If more than 20% of the responses to the total expected dose-taken prompts are checked "no," left blank, or missing, then the subject will be deemed noncompliant for dosing and a deviation recorded e.g., 12 checked "no," left blank, or missing at Visit 2 and Visit 3 and more than 24 at Visit 4.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the trial.

8.6.2 Discontinued subjects

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

- Adverse event;
- Protocol violation;
- Lack of efficacy;
- Administrative reason (e.g. inability to continue, lost to follow up);
- Sponsor termination of trial;
- Subject choice (e.g. withdrawal of consent);
- Other

Subjects must be discontinued as outlined in Section 5.6.
Subjects who discontinue for any reason after randomization will not be replaced.

8.7 Trial Termination

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g. due to:
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the sponsor's IMP.
- Terminated or suspended upon request of Health Authorities.

Health Authorities and Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

8.8 Trial Duration

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. The total duration of the trial from "first subject in" to "last subject out" is expected to be 7 months.

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject signature of the ICF without any judgment on causality.

If there is a worsening of a medical condition that was present prior to Visit 0, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the IMP that remains unchanged or improved should not be recorded as an AE at subsequent visits.

Worsening of DED will be considered an AE only if the dry eye status of the subject exceeds their previous experiences with the condition. This will be determined by the subject and the investigator.

A clinically significant visual acuity worsening (defined as an increase of 0.22 or greater in logMAR score) from screening (Visit 0) will be considered an Adverse Event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to IMP, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon non-leading AE questioning.

AEs (both elicited and observed) and SAEs will be monitored throughout the trial. The investigator will promptly review all AEs for accuracy and completeness. All AEs will be documented on the appropriate source document and eCRF.

Adverse events recorded from the signing of informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered study-related.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IMP or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the investigational drug should be determined by the investigator using these explanations:

- *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.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IMP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IMP exposure, but is otherwise uncommon in the population exposed to the IMP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the trial population independent of drug therapy) that indicates those events occur more frequently in the IMP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of a treatment emergent AE should be determined based upon existing safety information about the IMP. The active ingredient of NOV03 is perfluorohexyloctane, which is a semifluorinated alkane with a well-established tolerability and safety profile. It has been tested in four PMCF studies and one phase 2 clinical trial up to now with >370 subjects that received NOV03 treatment. AEs of those studies have been listed in the Investigator's Brochure. Therefore, the following definitions will be used:

- *Unexpected*: An AE that is not listed in the investigator's brochure in the Adverse Reaction Section at the specificity or severity that has been observed.
- *Expected*: An AE that is listed in the investigator's brochure in the Adverse Reaction Section at the specificity and severity that has been observed.
- *Not Applicable*: Any AE with an onset prior to first dose of IMP.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the sponsor's determination.

9.1.4 Outcome

The outcome of any AE will be determined and recorded using the following categories:

- Recovered/Resolved
- Recovering/Resolving

- Not Recovered/Not Resolved
- Recovered/Resolved with Sequelae
- Lost to Follow-up
- Fatal
- Unknown

9.2 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:

- Death;
- A life-threatening AE;
  - Note: An AE is considered "life-threatening" if, in the view of either the investigator, medical monitor or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;
  - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.
  - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g. hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect;
- Medically important
  - Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.3 Procedures for Reporting Serious Adverse Events

All AEs and their outcomes must be reported to CRO, the trial sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate source document and eCRF page.

9.3.1 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IMP, must be immediately (i.e. within a maximum 24 HOURS after becoming aware of the event) reported to CRO. All information relevant to the SAE must be recorded on the appropriate SAE report form. Within 24 hours of knowledge of a new SAE, the investigator must enter the SAE information onto the hard copy SAE report form and send the form to the [redacted] The investigator must verify that the report was received by CRO. If the investigator is not able to verify it was successfully received by CRO, the investigator must call the CRO clinical study manager by phone to follow-up. The CRO will forward the documentation to the medical monitor and the sponsor for review.

The information entered must contain sufficient information to enable medical assessment by the medical monitor. At a minimum, the initial SAE report should contain the following information:

- Subject's trial ID number
- Description of the Serious Adverse Event
- Date of the Serious Adverse Event
- Criterion for seriousness
- Preliminary assignment of causality to IMP

All information relevant to the SAE must be recorded on the appropriate case report forms. The investigator is obligated to pursue and obtain information requested by CRO, CRO and/or the sponsor in addition to that information reported on the case report form. All subjects experiencing a SAE must be followed up and the outcome must be reported.
The investigator must obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide CRO and the trial sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IMP; and inform the IRB of the AE within their guidelines for reporting SAEs.

All SAEs will be reported from the signature of Informed Consent until 30 days after the last administration of study drug.

All SAEs will be followed until resolution, stabilization, the event is otherwise, explained, or the subject is lost to follow-up.

Investigators are not obligated to actively seek SAE information from subjects that completed the study, but investigators are encouraged to notify the Sponsor, or designee, of any SAEs of which they become aware occurring at any time after a subject has discontinued or completed the study that they judge may be reasonably related to treatment with study drug.

9.3.2 Reporting a Suspected Unexpected Serious Adverse Reaction (SUSAR)

All SAEs that are 'suspected' and 'unexpected' are to be reported to CRO within 24 hours after the site becomes aware of the event, via the SAE reporting process outlined above. All SAE/SUSARs will be promptly reported to the IRB/IEC and governing health authorities (e.g., United States Food and Drug Administration [FDA]) as required by the IRB/IEC, federal, state, and local regulations and timelines.

9.4 Procedures for Unmasking of IMP

All subjects, investigators, and trial personnel involved with the conduct of the trial will be masked with regard to treatment assignments. The mask may be broken in exceptional circumstances.

In a medical emergency, when the management of a subject's condition requires knowledge of the treatment assignment, the investigator, or designee, will obtain the trial treatment assignment from the Interactive Response System (IRS). If possible, the medical emergency should be discussed with the medical monitor prior to obtaining the treatment assignment, or as soon after as possible. The sponsor may unmask for regulatory submission determination of an SAE when necessary (see Section 9.3.1).

In a non-emergency situation, when a code break is required, it must be discussed with the medical monitor and/or CRO and the trial sponsor. The code break must be approved in writing by the sponsor.

If the randomization code for a subject is broken, the investigator will record the date and reason for lifting the mask for that subject in the source documents. Upon unmasking, the subject will be withdrawn from the trial and should complete both the Early Termination and Follow-up procedures.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the investigator becomes aware of any new information regarding an existing SAE (i.e. resolution, change in condition, or new treatment), a new SAE Report Form must be completed and faxed to CRO within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered, but a new SAE Report Form must be completed and identified consecutively based on the previous report form (i.e. Initial Report, Follow-up #1, Follow-up #2, etc.). The report must describe whether the event has resolved or continues and how the event was treated.

9.6 Reporting Pregnancies

Pregnancy itself is not considered an AE or SAE (unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication). Pregnancy is an important medical event that must be followed up. Any pregnancy that occurs during the clinical trial where the fetus could have been exposed to IMP must be followed through the outcome of the pregnancy.

It is the responsibility of the Investigator to obtain the outcome and condition of the infant information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

If a subject or investigator suspects that the subject may be pregnant prior to IMP administration, the IMP must be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the subject must not receive IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is receiving IMP treatment, the IMP must immediately be withheld until the result of pregnancy testing is known.

If a female reports a pregnancy or has a positive pregnancy test during the trial, then the investigator must report the pregnancy and the outcome of the pregnancy to the CRO within 24 hours of learning about the pregnancy and outcome of the pregnancy respectively.

A Pregnancy Report Form will be completed by the trial site's principal investigator and and send the form to the [redacted]. The investigator must verify the report was received by CRO. If the investigator is not able to verify it was successfully received by CRO, the investigator must call the CRO clinical study manager by phone to follow-up. The CRO will forward the documentation to the medical monitor and the sponsor for review.

At the completion of the pregnancy, the Pregnancy Report Form is to be submitted to the CRO via the SAE contact details.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

Full Analysis Set (FAS) – 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.

Per Protocol Set (PPS) – 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.

Safety Set (SAF) – 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.

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.

10.2 Statistical Hypotheses

The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

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 NOV03 and 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 ≠ 0, with superiority claimed if the difference is less than 0 (NOV03 minus saline).

Hierarchical fixed sequence testing will be employed to maintain the type I error rate within the two primary endpoints. The primary analyses will first test the difference in the mean CFB corneal fluorescein staining (NEI scale) total score between treatments at Day 57. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of NOV03 then the trial will be considered a success; NOV03 will be declared to be superior to saline in the mean CFB corneal fluorescein staining (NEI scale) total score at Day 57; and the difference in the mean CFB total Dryness Score between treatments at Day 57 will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean CFB corneal fluorescein staining (NEI scale) total score at Day 57 is in favor of NOV03, and the test of the difference in the mean change from Dryness Score at Day 57 is also statistically significant in favor of NOV03, then NOV03 will be declared to be superior to saline in both the mean CFB corneal fluorescein staining (NEI scale) total score and the mean CFB of the Dryness Score at Day 57.

10.3 Sample Size

[redacted]

The study has been designed to have at least 95% power to reject both H_{01} and H_{02} assuming independence between the sign and symptom endpoint; positive correlation between these two endpoints would increase the overall power.

Two hundred fifty (250) subjects (study eyes) per treatment group yields 97.9% power to reject H_{01} in favor of H_{A1} 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}.

10.4 Statistical Analysis

10.4.1 General Considerations

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The qualitative variables will be summarized using counts and percentages.
All summaries will be presented by treatment group. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.
For the purpose of summarization, medical history, concurrent therapies, and AEs will be coded to MedDRA and WHO Drug dictionaries, as appropriate.
Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment.
All primary and secondary analyses will be two-sided at a significance level of 0.05.

10.4.2 Unit of Analysis

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

10.4.3 Missing Data

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 10.4.5 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.

The imputation model, for each visit, under the assumption of missing **at** random is:

```
PROC MI DATA=INDATA SEED=97656 OUT=OUTDATA1 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 corneal fluorescein staining score for each region (inferior, superior, central, temporal, and nasal).
The imputation model, for each visit, under the assumption of missing **not at** random is:

```
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 corneal fluorescein staining score for each region (inferior, superior, central, temporal, and nasal).

10.4.4 Multiplicity Consideration

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

10.4.5 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:

- Population: Subjects with DED defined through enrollment criteria
- 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]
- 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 is ≥5% then the primary analysis will be based on imputation methodology using the following estimands and the available data analyses will become robustness analyses.:

- Population: Subjects with DED defined through enrollment criteria
- 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 lack of efficacy or adverse events. Baseline observation carried forward (BOCF) is used to impute missing data [hypothetical strategy].
  - 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 is used to impute missing data [hypothetical strategy].
- 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 in Dryness Score (VAS) 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.

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 Akaike information criterion with a correction for finite sample sizes (AICc).

10.4.6 Secondary Efficacy Analyses

The following secondary endpoints will be tested hierarchically:

1. CFB of Dryness Score (VAS) at Day 15.
2. CFB in tCFS (NEI scale) at Day 15.
3. CFB VAS burning/stinging at Day 57.
4. CFB in central Corneal Fluorescein Staining (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 effiacy 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 10.4.5 and the available data analyses will become robustness analyses.

10.4.7 Other Pre-specified Efficacy Analyses

The analyses of other pre-specified endpoints will use the Full Analysis Set (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 Ocular Surface Disease Index (OSDI©) at each measured post-baseline visit.

Quantitative other pre-specified efficacy endpoints 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.

Two-sample t-tests, Wilcoxon rank sum tests and mixed-effect repeated measures analysis will also be presented as sensitivity analyses.

Other pre-specified 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. Pearson chi-squared analysis comparing the treatment groups will be performed as sensitivity analyses.

[redacted]

[redacted]

[redacted]

[redacted]

Exploratory and other endpoints will be summarized and analyzed similarly to the other pre-specified endpoints.

10.4.10 Safety Variables Analyses

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

Extent of Exposure

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.

Analysis of Adverse Events

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of trial treatment. Furthermore, frequencies will be

given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class, preferred term and strongest relationship; and by system organ class, preferred term, maximal severity, and strongest relationship. Separate summaries will be performed for ocular and non-ocular AEs.

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

Concomitant Medications

Concomitant medications will be coded using the most recent version of WHO-Drug Dictionary and summarized by treatment group.

Other safety endpoints including those assessed by visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

10.4.11 Interim Analyses

No interim analyses are planned for this trial.

10.5 Additional Analyses

No further analysis is planned.

10.6 Methods to Minimize Bias

This is a randomized treatment assignment, double-masked, multi-center trial. Subjects will be instructed not to show or discuss the properties of the assigned Investigational Medicinal Product (IMP) and/or their experience with the IMP with other trial participants, and not to show or discuss the IMP with the Investigator or site staff other than the dedicated dosing coordinator, unless instructed to do so.

A dedicated dosing coordinator at each site will be responsible for instructing subjects regarding IMP handling/administration, IMP dispensation and accountability, reviewing daily dosing diaries, performing the Instillation Comfort Questionnaire, the Eyedrop Acceptability Questionnaire and all discussions with study subjects related to IMP.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This trial will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IMPs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent must take place before any trial specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the trial.

All informed consent forms must first be approved by the sponsor and receive approval from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the trial as well as those currently enrolled in the trial, as recommended by the the governing IRB.

11.1.2 Institutional Review Board (IRB) Approval

This trial is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). Only an IRB/IEC approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal trial subject data collected and processed for the purposes of this trial should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of CRO, the sponsor, the IRB/IEC approving this trial, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct

access to the trial subject's original medical and trial records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the IMP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's trial subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The investigator's electronic copy of the eCRFs serves as the investigator's record of a subject's trial-related data.

11.4.1 Retention of Documentation

All trial related correspondence, subject records, consent forms, record of the distribution and use of all IMP and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator must notify the sponsor prior to destroying trial documentation even after the above-mentioned time has passed.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

All subject data will be captured in the subject source documents which will be entered into the eCRFs in the Electronic Data Capturing System (EDC). The investigator is responsible for ensuring that trial data is completely and accurately recorded in the source documents, data entered into each subject's eCRF, and all trial-related materials. All trial data should also be attributable, legible, contemporaneous, and original. Recorded data should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data).

The EDC system is conforms to 21 CFR Part 11 requirements and data entry into the system will be performed only by staff that have been trained and have access to the system. An audit trail will be maintained within the system to capture all changes made within the database. After the end of the trial and database lock, copies of all applicable subjects' eCRFs will be provided to each investigator site to be maintained on file by the investigator.

11.6 Monitoring and Quality Assurance

During the course of the trial a clinical research associate (CRA) will make routine site visits to review protocol compliance, assess IMP accountability, and ensure the trial is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the trial monitoring (including medical monitoring) will be outlined in a monitoring plan.

Domestic and foreign regulatory authorities, and quality assurance, sponsor and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out with consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

11.7 Handling of Biological Specimens

Not applicable.

11.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the trial. Authorship will be established before writing the manuscript. The trial sponsor will have the final decision regarding authorship, manuscript and publication.

12 REFERENCES

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13 APPENDICES

Appendix 1 Schedule of Assessments (in recommended order)

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				
Previous/Concomitant Medication	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X			
Urine Pregnancy Test	X	X			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	
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

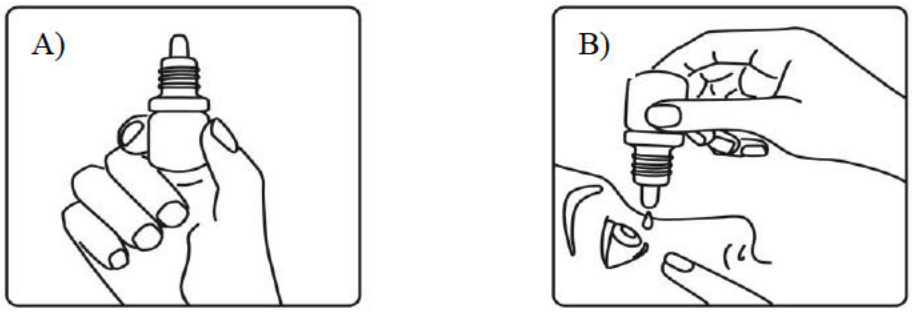
Appendix 2 Instructions for Administration of Eye Drops

Instructions for Use

Subjects will be instructed to instill one drop in each eye four times daily as illustrated below. Subjects will be instructed to use a second drop only if the first drop misses the eye. Subjects will be given detailed instructions on study drug administration (see below), accountability, and storage.

Note: On day of study Visits 2, 3 and 4, subjects should make sure that their dose of the study drug is instilled at least 2 hours before the start time of the visit.

Proper Handling of Eye drop Container



Note: Please contact study site staff immediately for replacement if you notice any damage with study drug container.

Figure A. Opening the bottle

1. Unscrew the cap of the bottle.
2. Prior to the first administration of the study drug you must separate the cap from the safety seal ring below the cap and remove it.
3. Do not touch the dropper after removing the cap.
4. To avoid loss of solution **please read steps 5 to 7** carefully before applying the eye drops.
5. Hold the opened bottle with the dropper pointing upwards and gently press the bottle between thumb and index finger.
6. Keep the bottle under slight pressure and turn the bottle until the dropper points downwards.
7. With the dropper pointing downwards reduce the pressure on the bottle to allow some air to flow into the bottle.

Figure B. Instilling the drop

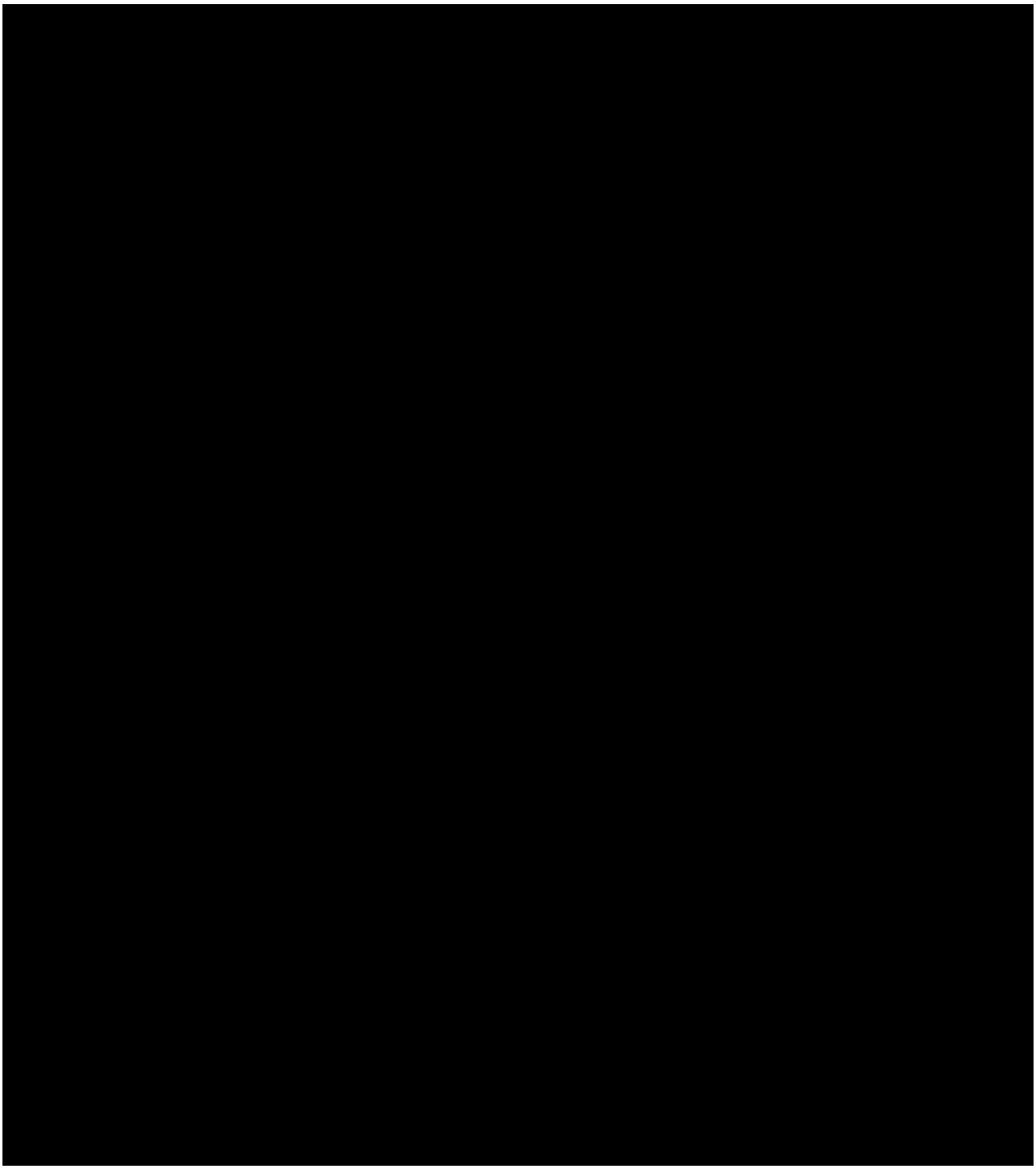
1. Lean your head back slightly and carefully pull down your lower eyelid. Look upwards.
2. Hold the opened bottle with the dropper pointing downwards above your eye. Apply gentle pressure on the bottle and administer 1 drop per eye.

Note: Due to the special properties of the study drug you may not feel the drop falling into your eye. In this case we recommend application in front of a mirror.

3. Do not touch the dropper with your eye or lashes.
4. For an even distribution, close your eyes after applying the study drug.

5. Put the screw cap back on after administration.

If a subject has difficulties with step 4 to 7 of Figure A, advise to refer to step 2 of Figure B: subject to squeeze bottle very gently or to wait until drop drips from the bottle without squeezing.



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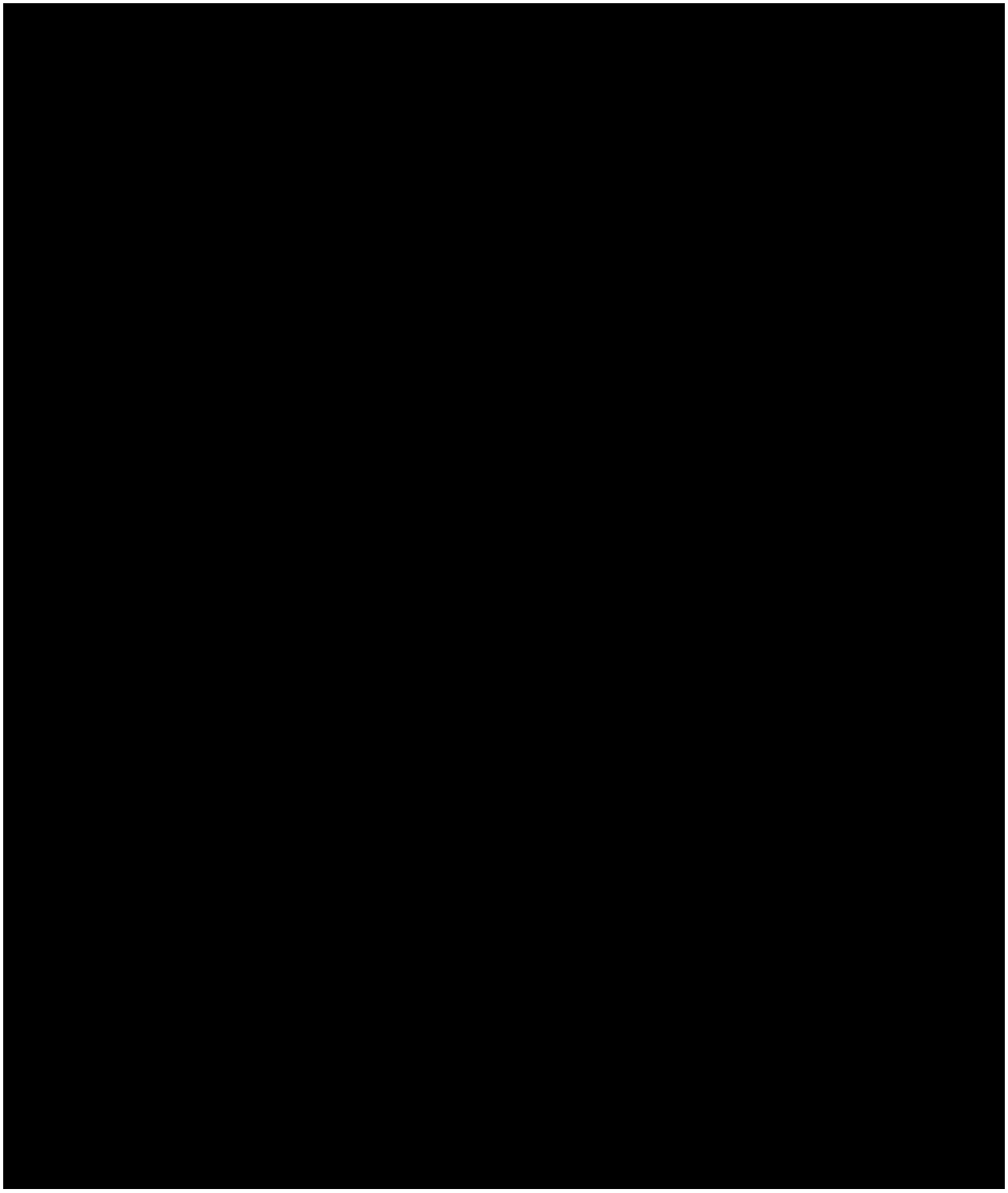

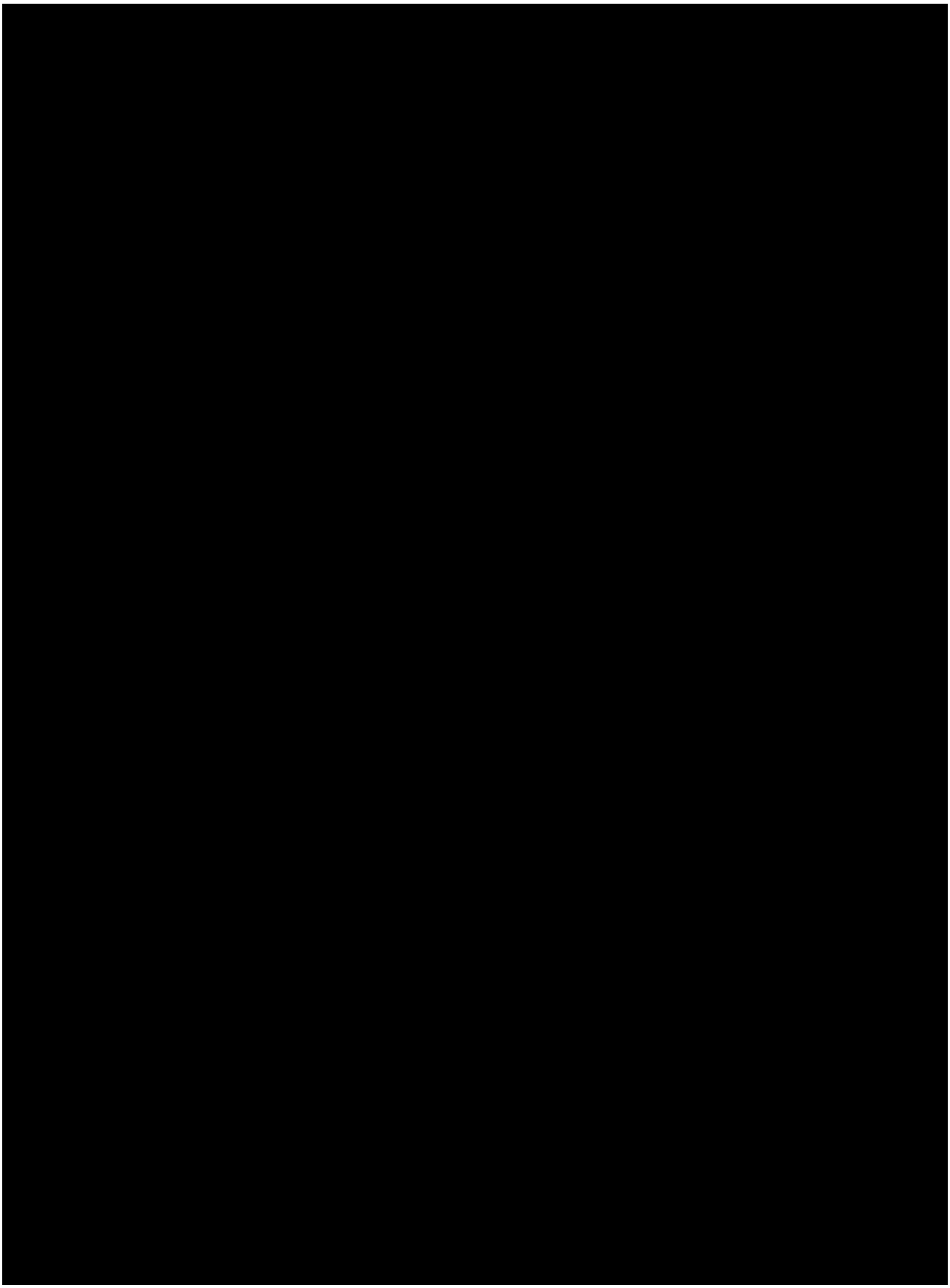

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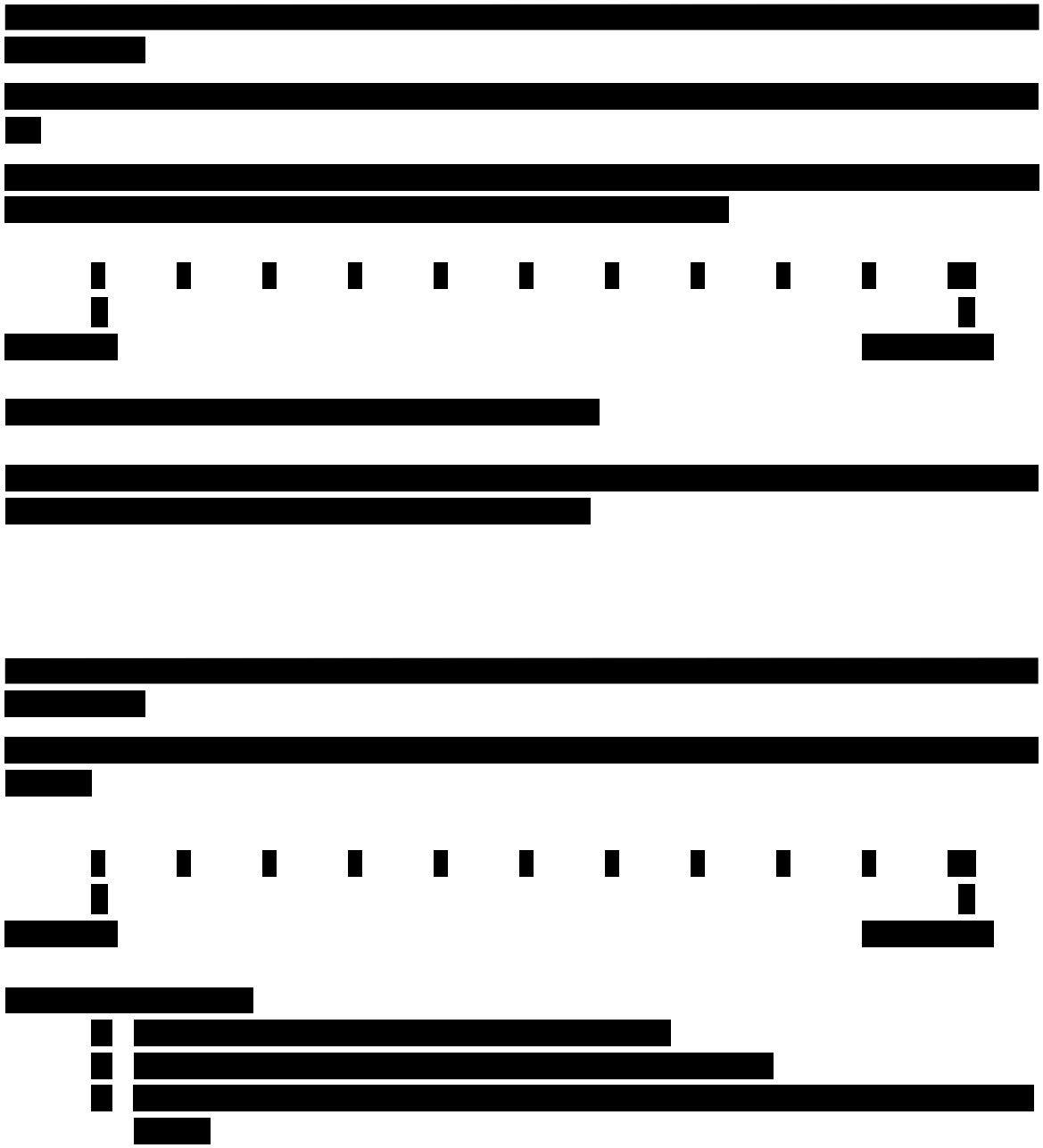

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Appendix 4 Amendment Summary of Changes

Page	Original Text	Amended Text (in bold)	Rationale
1	Version 1.0	Version **2.0**	New version of protocol
1		**Amendment 1: 09 NOV 2020**	Generation of Amendment 1
2	[redacted]	[redacted]	Correction
5, 27	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.	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 (e.g. Botox injections for blepharospasm).**	Added clarification
7, 28		**31. Have a history of isotretinoin (e.g. Accutane, Myorisan, Claravis, Amnesteem) use.**	Added
36		• History of isotretinoin use	Added
43	The expectedness of an AE should be determined based upon existing safety information about the IMP.	The expectedness of a **treatment emergent** AE should be determined based upon existing safety information about the IMP.	Clarification
43	• *Not Applicable*: Any AE that is unrelated to the IMP.	• *Not Applicable*: Any AE **with an onset prior to first dose of** IMP.	Clarification
73		**Appendix 4: Summary of Changes**	Added
74		**Amendment 1 Date: 09 NOV 2020**	Generation of Amendment 1
75		**Amendment 1 Date: 09 NOV 2020**	Generation of Amendment 1

Appendix 5 Sponsor and CRO Approvals

Protocol 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 (Mojave Study)
Protocol Number:	904
Date:	05 AUG 2020
Amendment 1 Date	09 NOV 2020

[redacted]

mk 12/1/2020

Appendix 6 Investigator's Signature

Protocol 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 (Mojave Study)
Protocol Number:	904
Date:	05 AUG 2020
Amendment 1 Date:	09 NOV 2020

I agree to implement and conduct the trial diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by CRO and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____