Clinical Trial Protocol

Protocol Title:	A Phase 2, Multi-Center, Randomized, Double-Masked, Saline-Controlled Study to Evaluate the Effect of Perfluorohexyloctane (NOV03) at Two Different Dosing Regimens on Signs and Symptoms of Dry Eye Disease.
Protocol Number:	NVU-002
Study Phase:	2
Product Name:	NOV03 ([redacted] Perfluorohexyloctane)
IND Number:	130588
Indication:	Dry Eye Disease (DED)
Sponsor:	NOVALIQ GmbH Im Neuenheimer Feld 515 69120 Heidelberg Germany
Contract Clinical Research Organization	[redacted]
Version:	2.0
Amendment 1:	07 December 2017
Original Protocol Date:	13 October 2017

Regulatory Statement

This study will be performed in compliance with the protocol and in accordance with Good Clinical Practice (International Conference on Harmonisation [ICH], Guidance E6, 1996), principles of human subject protection, and applicable country-specific regulatory requirements.

STUDY CONTACT INFORMATION

NOVALIQ GmbH

Role in the Study	Name and Contact Information
Manager Clinical Development:	[redacted]
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MEDICAL MONITOR

Medical Monitor:	[redacted]

PRODUCT SAFETY

Sr. Product Safety Associate:	[redacted]

SYNOPSIS

Protocol Title:	A Phase 2, Multi-Center, Randomized, Double-Masked, Saline-Controlled Study to Evaluate the Effect of Perfluorohexyloctane (NOV03) at Two Different Dosing Regimens on Signs and Symptoms of Dry Eye Disease
Protocol Number:	NVU-002
Study Drug:	NOV03 ([redacted] Perfluorohexyloctane)
Control:	Saline solution: 0.9% sodium chloride solution
Study Phase:	2
Study Objective:	The primary objective for this study is to evaluate the efficacy, safety, and tolerability of perfluorohexyloctane (NOV03) at two different dosing regimens compared to saline solution in subjects with Dry Eye Disease. [redacted]
<u>Overall Study Design</u>	
Structure:	Multi-center, randomized, double-masked, saline-controlled
Duration:	An individual subject's participation is estimated to be approximately 10 weeks.
Dosage/Dose Regimen:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally from Visit 1 to Visit 4. 1) NOV03 ([redacted] Perfluorohexyloctane) 4 times daily (QID) 2) NOV03 ([redacted] Perfluorohexyloctane) 2 times daily (BID) 3) Saline solution (0.9% sodium chloride solution) QID 4) Saline Solution (0.9% sodium chloride solution), BID

Summary of Visit Schedule:	5 visits over the course of approximately 10 weeks • Visit 0 = Within 14 days before Visit 1, Screening • Visit 1 = Day 1, Baseline/Randomization • Visit 2 = Day 15 ± 1 days, 2-week follow-up • Visit 3 = Day 29 ± 2 days, 4-week follow-up • Visit 4 = Day 57 ± 2 days, 8-week follow up /Study Exit
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double-masked, multi-center study.
<u>Study Population Characteristics</u>	
Number of Subjects:	Approximately [redacted] subjects will be screened to enroll at least 300 subjects (100 each for the two active arms, and 50 each for the two saline solution arms) subjects at up to 15 sites.
Condition/Disease:	Dry Eye Disease (DED)
Inclusion Criteria:	**Subjects must:** a. Be at least 18 years of age. b. Provide written informed consent. c. Have a subject reported history of Dry Eye Disease [redacted]. d. Have Tear film break-up time (TFBUT) [redacted] at Visit 0 and Visit 1. e. Have Ocular Surface Disease Index (OSDI©) [redacted] at Visit 0 and Visit 1. f. Have a Schirmer's Test I [redacted] mm at Visit 0 and Visit 1. g. Have Meibomian Gland Dysfunction (MGD) defined as MGD score [redacted] at Visit 0 and Visit 1.

	h. Have a total corneal fluorescein staining score of [redacted] i. Have at least one eye (the same eye) satisfy all criteria for d, f, g, and h above at Visit 0 and Visit 1. j. Be able and willing to follow instructions, including participation in all study assessments and visits.
Exclusion Criteria:	**Subjects must not:** a. Have any clinically significant slit-lamp findings at Visit 0 and/or in the opinion of the investigator have any findings that may interfere with study parameters, and may include eye trauma or history of eye trauma. [redacted] e. Have abnormal lid anatomy (incomplete eyelid closure, entropion, ectropion) that exposes parts of the conjunctiva or impairs the blinking function of the eye. [redacted]

	[redacted] [redacted] h. Have an ocular or periocular malignancy. [redacted] j. Have a history of herpetic keratitis. k. Have active ocular allergies or ocular allergies that are expected to be active during the study period. l. Be diagnosed with an ongoing ocular or systemic infection (bacterial, viral, or fungal), including fever and current treatment with antibiotics. m. Have worn contact lenses within 1 month of Visit 0 or anticipate using contact lenses during the study. [redacted] [redacted] p. Be a woman who is pregnant, nursing or planning a pregnancy. q. Be unwilling to submit to a blood pregnancy test at Visit 0 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). r. 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 study, she must agree to use adequate birth control as defined above for the remainder of the study. s. Have an uncontrolled systemic disease. t. Have a known allergy and/or sensitivity to the study drug or saline components. [redacted] [redacted] w. Have used any topical steroids treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0. [redacted] y. Have corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution (logMAR), [redacted] as assessed by Early Treatment of Diabetic Retinopathy Study

	(ETDRS) scale in both eyes at Visit 0 and Visit 1. z. 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 study results, or may interfere significantly with the subject's participation in the study.
Study Formulations:	• [redacted] Perfluorohexyloctane • Saline Solution (0.9% sodium chloride solution)

Evaluation Criteria	
Efficacy Endpoint(s):	**Primary Efficacy Endpoints:** The following primary endpoints will be tested: • Corneal Fluorescein Staining (CFS) total (NEI grading) [redacted]

	[redacted]
Safety Endpoints:	• Visual Acuity. • Slit-Lamp Biomicroscopy. • Intraocular Pressure. • Dilated Fundoscopy. • Hematology/Chemistry parameters. • Systemic and ocular adverse events. • Symptoms directly related to the instillation or use of the investigational medication based on questionnaire/visual analogue scale.
Other:	• Pharmacokinetics of perfluorohexyloctane (blood levels for perfluorohexyloctane at predefined time points and PK parameters as appropriate).

General Statistical Methods and Types of Analyses

Sample Size

At least 300 subjects (100 each for the two active arms, and 50 each for the two saline solution arms) will be randomly assigned to study treatment such that approximately 90 evaluable participants per active arm and 45 per saline solution arm complete the study, assuming a 10% dropout rate.

Primary Efficacy Analyses:

The primary evaluation of efficacy of the active arms will be against a combined control arm (with BID and QID saline solution). Sensitivity analysis may be undertaken for dosing-regimen matching control (that is, QID active vs. QID saline solution).

The primary analysis will be performed to compare the week 8 difference in the change from baseline in CFS between the active NOV03 groups and the saline solution groups. The comparison will be conducted using a repeated measures model with treatment, site, visit, and treatment by visit interaction fixed categorical factors, baseline as a continuous covariate, and using an unstructured covariance matrix. To establish evidence of efficacy in this proof of concept study, the hypothesis tests will be one-sided and performed at the 0.05 significance level.

[redacted]

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 patient signed Informed Consent Form (ICF). 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.

Pharmacokinetics

Whole blood for perfluorohexyloctane blood concentration measurements will be drawn from a minimum of 66 subjects at least at one investigational site with the goal of having samples from 20 subjects per treatment arm. Blood concentrations of perfluorohexyloctane will be summarized descriptively. If possible, the following PK parameters will be estimated: $AUC_{0-\tau}$, C_{max}, t_{max} and summarized descriptively.

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LIST OF ABBREVIATIONS

AE	adverse event
$AUC_{0\text{-last}}$	Area under the blood concentration time curve from time 0 to time of last measureable concentration
BAC	benzalkonium chloride
BCVA	best-corrected visual acuity
BID	Two times daily
CFR	Code of Federal Regulations
C_{max}	Maximum blood concentration
CRF	case report form
CV	Coefficient of variation
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
eCRF	electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	investigational new drug
IOP	intraocular pressure
IRB	institutional/independent review board
IUD	Intra-uterine device
IWRS	interactive web response system
logMAR	logarithm of the minimum angle of resolution
LLT	lipid layer thickness
LS mean	Least square mean
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
mITT	modified intent-to-treat
NEI	National Eye Institute
NOV3	[redacted] perfluorohexyloctane
OD	right eye
OS	left eye
OSDI©	ocular surface disease index
PP	per protocol
QID	four times a day
SAE	serious adverse event
SAP	Statistical Analysis Plan

TEAEs	Treatment-emergent adverse events
TFBUT	tear film break-up time
TFT	tear film thickness
t_{max}	time to C_{max}
VA	visual acuity
VAS	visual analog scale

1 INTRODUCTION

1.1 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.[2] 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.[4,5,6] 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.[1]

1.2 Product Rationale

NOV03 is a sterile ophthalmic eye drop formulation, developed for the treatment of the signs and symptoms of DED associated with meibomian gland dysfunction (MGD).

It is a one component product consisting of [redacted] perfluorohexyloctane developed to supplement the lipid layer leading to reduced evaporation of the tear film and thereby protecting the ocular surface. As a single component product, it is free of excipients like oils, surfactants and preservatives. NOV03 is developed with the goal to provide patients with DED due to MGD an effective treatment option with a new mode of action addressing directly the lipid layer. Further advantages compared to existing therapies including convenient handling, improved tolerability, and a decrease in the visual disturbance associated with oily eye drops, emulsions or ointments.

The sole ingredient of NOV03 is the anhydrous semifluorinated alkane, perfluorohexyloctane [redacted]. Liquid semifluorinated alkanes are physically, physiologically and chemically inert, colorless, laser stable compounds with the same refractory index as water. They do not undergo metabolism in the human body.[3] Perfluorohexyloctane shows a low surface tension of 19.65 mNm, which leads to excellent spreading activities on the ocular surface and to the formation of small droplet. On the ocular surface, NOV03 forms a thin film together with tear lipids thereby supporting the lipid layer, which in its natural function to reduce the evaporation of the tear film and reducing sharing forces.

1.3 Trial Rationale

NOV03 might be valuable for patients with DED due to MGD, as the loss of the lipid layer in these patients leads to increased evaporation of the tears. Initial clinical data from observational studies NT-001[7] and NT-002[8] consistently indicate that NOV03 is efficacious in treating signs and symptoms of mild to moderate evaporative DED and mild to moderate

DED and MGD. A mechanistic clinical study NT-004 demonstrated that NOV03 increase tear film thickness (TFT) and lipid layer thickness (LLT) over saline solution, and therefore provides further clinical evidence supportive for this indication.

This first US study is designed to investigate the efficacy and safety in a larger population versus a control in a double masked fashion. It is powered to demonstrate efficacy for a sign endpoint total CSF (NEI grading). Other sign and symptom endpoints will be explored as well as the dosing regimen.

Data from this study will serve to plan the phase 3 program for the project.

1.4 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. Perfluorohexyloctane has been on the market as a medical device in the European Union for more than 10 years in ophthalmology, approved as a temporary endotamponade and an intraoperative instrument for retinal surgery. It is not yet approved in the US. Physical properties such as low surface and interface tension, colorlessness and notably complete physical and chemical inertness make this substance class suitable for the topical ophthalmic application.

A total of 151 subjects have been treated with NovaTears® (NOVALIQ GmbH, Heidelberg, Germany) in four post-marketing studies, with a treatment duration between 4 and 12 weeks.

Safety and local tolerability of NovaTears® during these four post marketing studies was found to be excellent when used at the recommended dose of one drop per eye, 4 times a day. In all four studies, no changes in intraocular pressure (IOP) or best-corrected visual acuity (BCVA) was observed, nor were clinically significant findings with slit lamp examinations. Out of a total of 151 patients across four post market studies, 27 AEs were reported from 17 subjects treated with NovaTears®, 12 of which were considered possibly, probably or definitely related to the use of NovaTears®. All cases reported to be related described symptoms of mild to moderate ocular irritation, which disappeared shortly after discontinuation of the product. No serious adverse events (SAEs), incidents or deaths occurred.

Furthermore, market vigilance data collected to date from >1 million bottles dispatched in the market confirms the good safety profile, with only 64 medical complains as of 30 June 2017. The vast majority of these medical complaints were mild cases of ocular irritations.

The observational studies consistently indicate that NOV03 is efficacious in treating signs and symptoms of mild to moderate evaporative DED and mild to moderate DED caused by MGD. A statistically significant increase in tear film fluid was observed in study NT-001, while tear film stability, as assessed by TFBUT, was shown to significantly improve in both the NT-001 and NT-002 studies. Comparable to these results, a significant decrease in the average OSDI© score was also observed in studies NT-001 and NT-002 together with decreases in the intensity of corneal staining (and conjunctival staining in NT-002). No

change was observed for any of these parameters in NT-003 in patients with DED due to GvHD. Study NT-004 demonstrated that NovaTears® increase TFT and LLT over saline solution, and therefore provides further clinical evidence supportive of the mode of action of NovaTears®.

In summary, based on the preclinical and clinical data obtained to date, risks to subjects in the planned NVU-002 study are considered very low. Furthermore, the subjects randomized in the study will be closely monitored, and current standard ophthalmological safety assessments will be performed during the entire treatment period in the study at 2, 4 and 8 weeks. The efficacy demonstrated to date is supportive of increased benefits in addressing the evaporative aspects of DED by strengthening the lipid layer, and suggests relief of DED symptoms and signs, that is possibly more sustainable than comparator saline treatments. NOV03 therefore provides a favorable risk-benefit treatment profile to patients with mild to moderate DED and the NVU-002 study is designed to further assess this positive profile.

2 STUDY DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

- The primary objective for this study is to evaluate the efficacy, safety, and tolerability of perfluorohexyloctane (NOV03) at two different dosing regimens compared to saline solution in subjects with Dry Eye Disease

[redacted]

2.1.3 Primary Endpoints

- Total CFS (NEI Grading Scale) at Day 57.

[redacted]

[redacted]

2.2 Overall Study Design and Investigational Plan

This study is a phase 2, multi-center, randomized, double-masked, saline-controlled study to evaluate the effect of NOV03 ([redacted]perfluorohexyloctane) at two different dosing regimens on signs and symptoms of Dry Eye Disease. Approximately 300 male and female subjects of at least 18 years of age with a subject-reported history of DED in both eyes and who meet all other study eligibility criteria will be randomized, stratified by site, 2:2:1:1 to receive 1 of 4 treatments:

Treatment 1: NOV03 ([redacted] Perfluorohexyloctane), 4 times daily (QID)

Treatment 2: NOV03 ([redacted]Perfluorohexyloctane), 2 times daily (BID)

Treatment 3: Saline (0.9% sodium chloride solution), QID

Treatment 4: Saline (0.9% sodium chloride solution), BID

Each active treatment group will be comprised of 100 subjects and each saline group will be comprised of 50 subjects such that approximately 90 evaluable subjects per active arm and 45 per saline arm complete the study. Up to 15 sites are anticipated to participate.

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

2.3 End of Study Definition

The end of the study for an individual patient is defined as that patient's last clinic visit. The end of the study for the overall trial is defined as the finalization of the Clinical Study Report.

2.4 Visit Description

Refer to Appendix 1 for the Schedule of Visits and Measurements and Table 1 for the Study Flow Chart.

Screening (Visit 0)

Subjects will be required to sign an Informed Consent before completing any study related procedure. At the screening visit, vital signs will be assessed and the subject will give blood for safety laboratory tests. They will also submit to a battery of tests to confirm the extent and severity of their symptoms and objective signs of dry eye. At least one eye must qualify with the following objective measures: Tear film break up time [redacted], Schirmer's Test [redacted], and Meibomian gland dysfunction (MGD) defined as MGD score [redacted].

Subjects who fail to qualify for the study at screening may be rescreened as described in section 3.5

Baseline Visit Day 1 (Visit 1)

On Day 1 (Visit 1), eligible subjects will be evaluated for baseline signs and symptoms of dry eye disease. After randomization subjects at selected sites will give a blood sample to be used for PK. Subjects will be given a 14-day supply and will self-administer a single drop of the study medication into each eye at the clinic. Each subject will be given a diary to record that their doses were taken. Study staff will help the subject to understand how to use the diary and when the remaining doses should be taken.

Visits 2-4

Subjects will return to the clinic on Day 15±1 (Visit 2), 29±2 (Visit 3), and 57±2 (Visit 4) to be evaluated for signs and symptoms of dry eye disease. During this period, subjects will dose NOV03 or the saline solution QID and BID, depending on their assigned group. The unused portion of the study medication should be returned to the clinic and a new study medication kit will be dispensed. The diary will be checked. At Visit 4, vital signs will be evaluated and a second blood draw will be performed for PK at selected sites. The diary will be collected at the clinic during each visit. Subjects will be dismissed from the study after all Visit 4 assessments have been completed.

Early Termination

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

2.5 Study Flow

All subjects will be expected to progress from screening through study exit. [redacted] There are no other side studies and all subjects will be evaluated according to Table 1:

Table 1. NVU-002 Study Flow Chart

Visit 0 (Within 14 days before Visit 1): Screening	Informed Consent (incl. HIPAA) Demographics, Medical/Medication & Ocular History, AE Query Symptom Questionnaires, Visual Acuity Eye Evaluations IOP / Dilated Fundoscopy Blood pressure and heart rate Blood Draw for Safety Labs (including pregnancy tests)
Visit 1 (Day 1): Baseline/Randomization	Medical/Medication Update: AE Query Symptom Questionnaires, Visual Acuity Eye Evaluations Randomization PK Predose Blood Draw (specific sites only) Study Drug Dispensed PK Postdose Blood Draws (specific sites only)
Visit 2 (Day 15 ± 1): 2-week follow-up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaires, Visual Acuity Eye Evaluations Study Drug Dispensed
Visit 3 (Day 29 ± 2): 4-week follow-up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaires, Visual Acuity Eye Evaluations, IOP Study Drug Dispensed
Visit 4 (Day 57 ± 2) 8 –week follow up / Study Exit	Collection of Study Drug/Diary Medical/Medication Update: AE Query Blood pressure and heart rate Symptom Questionnaires, Visual Acuity Eye Evaluations IOP / Dilated Fundoscopy Blood Draw for Safety Labs (including pregnancy tests) PK Blood Draw at the end of the visit (specific sites only)
HIPAA = Health Information Portability and Accountability Act IOP = intraocular pressure AE = adverse event PK = pharmacokinetic	

2.6 Enrollment and Treatment Assignment

All dose groups will be enrolled in parallel. Each subject will be assigned a unique screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion and exclusion criteria are met at Visits 0 and 1, each qualifying subject will then be assigned a randomization number. Once a randomization number has been assigned it must not be reassigned. [redacted] The Interactive Web Response System (IWRS) will be used to account for the stratification factor while assigning the randomization number. The subjects, investigators and sponsor will be masked to study treatment assignment.

Each subject will spend approximately 10 weeks in the study. The total duration of the study from first patient in to last patient out is expected to be 24 weeks (6 months).

3 STUDY POPULATION

3.1 Number of Subjects (approximate)

It is estimated that approximately [redacted] subjects will be screened. At least 300 participants will be randomly assigned to study treatment such that approximately 90 evaluable subjects per active arm and 45 per saline arm complete the study.

3.2 Study population characteristics

All subjects must be at least 18 years of age, and may be of either gender, and of any race. Subject must meet all inclusion criteria and none of the exclusion criteria.

3.3 Inclusion Criteria

Subjects will be eligible to participate in this study if they **meet all** of the following criteria

a. Male or female subjects, of age ≥18 years (inclusive) at the time of signing the informed consent form (ICF).

b. Provide written informed consent.

c. Have a subject reported history of Dry Eye Disease [redacted]

d. Have Tear Film Break Up Time [redacted] sec. at Visit 0 and Visit 1.

e. Have Ocular Surface Disease Index (OSDI©) [redacted] at Visit 0 and Visit 1.

f. Have a Schirmer's Test I [redacted] mm at Visit 0 and Visit 1.

g. Have Meibomian Gland Dysfunction defined as MGD score [redacted] at Visits 0 and 1.

h. Have a total corneal fluorescein staining score of [redacted]

i. Have at least one eye (the same eye) satisfy all criteria for d, f, g, and h above at Visit 0 and Visit 1.

j. Be able and willing to follow instructions, including participation in all study assessments and visits.

3.4 Exclusion Criteria

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

a. Have any clinically significant slit-lamp findings at Visit 0 and/or in the opinion of the investigator have any findings that may interfere with study parameters and may include eye trauma or history of eye trauma.

[redacted]

[redacted]

[redacted]

e. Have abnormal lid anatomy (incomplete eyelid closure, entropion, ectropion) that exposes parts of the conjunctiva or impairs the blinking function of the eye.

[redacted]

[redacted]

h. Have an ocular or periocular malignancy.

[redacted]

j. Have a history of herpetic keratitis.

k. Have active ocular allergies or ocular allergies that are expected to be active during the study period.

l. Be diagnosed with an ongoing ocular or systemic infection (bacterial, viral, or fungal), including fever and current treatment with antibiotics.

m. Have worn contact lenses within 1 month of Visit 0 or anticipate using contact lenses during the study.

[redacted]

[redacted]

p. Be a woman who is pregnant, nursing or planning a pregnancy.

q. Be unwilling to submit to a blood pregnancy test at Visit 0 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).

r. 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; intra-uterine 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 study, she must agree to use adequate birth control as defined above for the remainder of the study.

s. Have an uncontrolled systemic disease.

t. Have a known allergy and/or sensitivity to the study drug or saline components.

[redacted]

[redacted]

w. Have used any topical steroids treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0.

[redacted]

y. Have corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution (logMAR) [redacted] as assessed by the Early

Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 0 and Visit 1.

z. Have a condition or be in a situation (including language barrier) that the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

3.5 Re-Screen Procedures

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

3.6 Subject Withdrawal Criteria

Subjects may discontinue their participation in the study at any time without prejudice to further treatment.

A subject may be discontinued after randomization from the study for any of the following reasons:

- Noncompliance with the protocol as judged by the Investigator and/or the Sponsor;
- Incorrect enrollment of the subject (requires discussion with the Sponsor);
- If at any time during the study 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 AEs that present an unacceptable consequence or risk to the subject in the judgment of the Investigator, Sponsor, or the Medical Monitor;
- Occurrence of pregnancy;
- Withdrawal of consent.

4 STUDY PARAMETERS

4.1 Efficacy Measures

4.1.1 Primary Efficacy Variables

The following primary endpoints will be tested:

- Corneal Fluorescein Staining (CFS) total (NEI Grading Scale)

[redacted]

4.2 Safety Measures

- Visual Acuity
- Slit-Lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy
- Hematology/Chemistry parameters
- Systemic and ocular AEs
- Symptoms directly related to the instillation or use of the investigational medication based on questionnaire/visual analogue scale

4.3 Other

- Blood levels of perfluorohexyloctane at predefined time points.

5 STUDY MATERIALS

5.1 Study Drug(s)

5.1.1 Formulations

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

Table 2. Active Investigational Product

	Investigational Product
Product code:	NOV03
Chemical name:	Perfluorohexyloctane
Molecular formula:	[redacted]
Dosage form:	3 mL ophthalmic solution
Unit dose	[redacted] perfluorohexyloctane
Route of administration	Topical ocular administration
Physical description	Colorless and clear ophthalmic solution
Excipients:	None
Manufacturer:	[redacted]

Table 3. Control/Reference Investigational Product

	Control/Reference Investigational Product
Product name:	Saline solution
Chemical name:	Sodium chloride solution (0.9%)
Molecular formula:	[redacted]
Dosage form:	3 mL ophthalmic solution
Unit dose	[redacted]
Route of administration	Topical ocular administration
Physical description	Colorless and clear ophthalmic solution
Excipients:	[redacted]
Manufacturer:	[redacted]

5.2 Study Drug Storage

The study drugs must be stored in a secure area accessible only to the investigator and his/her designees. Study drugs must be stored **at room temperature** and must not be refrigerated. The investigational product must be protected from light, and secured at the investigational site in a locked container. Subjects should be instructed to store study drug in the same manner at home. Subjects should not use dispensed bottle that has been opened for more than 30 days. However, this may be prolonged at the discretion of the Investigator due to visit schedules.

Study medication shall be stored under temperature-controlled conditions with accessibility only to pharmacy staff and the site pharmacist who is authorized to dispense it to the subject.

5.3 Study Drug Preparation

When instructed by the investigator, or designee, the clinical staff will dispense one kit containing 2 bottles for each subject on Days 1 and 15 (± 1), and two kits on Day 29 (± 2). Subjects will be instructed on appropriate hygiene and eye drop dosing technique for multiple use drops by clinic staff. Subjects will self-administer NOV03 or Saline eye drops under the supervision of the medication coordinator on Day1 (Visit 1) as shown in Appendix 2. The bottles are designed for multiple use.

5.4 Administration of Study Drug

On Day 1 the first dose of drops will be instilled by the subject during the first clinic visit. During Days 2 through 57 (±2), subjects will be instructed to instill their drops into both eyes BID or QID. Clinic staff will coach the subjects to dose themselves at approximately the same time every day ± 1 hour. If a dose is missed, then the next dose should be administered on time.

5.4.1 Dispensation Schedule

- Study drug will be provided to sites as subject kits containing 2 bottles of NOV03 or saline solution.
- At the end of Visit 1, qualified subjects will be randomized and the first dose of study drug will be administered in the study center. The subject will receive the first subject kit. Subjects will be instructed to only open one bottle at a time. They should be instructed not to discard the empty bottles but return them at their next visit. Subjects will record in their diary that their doses were taken.
- At Visit 2, used/unused study drug will be collected from subjects for drug accountability. The subject will be dispensed a new subject kit to continue daily dosing. Subjects will be instructed to only open one bottle at a time. They should be instructed not to discard the empty bottles but return them at their next visit. Subjects will record in their diary that their doses were taken.
- At Visit 3 used/unused study drug will be collected from subjects for drug accountability. Subjects will receive two subject kits. Subjects will be instructed to only open one bottle at a time. They should be instructed not to discard the empty bottles but return them at their next visit. Subjects will record in their diary that their doses were taken.
- At Visit 4 used/unused study drug will be collected from subjects for drug accountability.
- Subjects will be instructed to immediately contact the site if there is any problem with the study drug, e.g. kit/bottle(s) was damaged or lost or if the open bottle was dropped. In case the subject needs a replacement, a new kit is assigned to the subject.

5.5 Study Drug Accountability

All study medication that is used during the course of the study must be accounted for on a drug accountability form. Investigational study medication orders, records of receipts, dispensing records, and inventory forms will be examined and reconciled. 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 study drug cartons (kits and their components) sent to the site, the amount used and unused at the time of reconciliation. No investigative drugs or kits will be discarded prior to full accountability by Sponsor's monitor.

Study drug shipment records will be verified and accountability performed by comparing the shipment inventory sheet to the actual quantity of drug bottles received at the site. Accurate records of receipt and disposition of the study drug (e.g. dates, quantity, subject number, kits used, kits unused, etc.) must be maintained by designated site personnel.

5.6 Study Drug Handling and Disposal

Unless otherwise directed, at the end of the study all unused investigational medications must be directly shipped from the clinical site to the disposal facility to dispose of the medications. **Note: The medications should not be disposed of prior to full accountability by the sponsor's monitor.** The clinical site will provide a copy of all completed drug disposition forms to the sponsor after the completion of the study.

6 STUDY METHODS AND PROCEDURES

6.1 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

Therapies such as lid scrubs, lid wipes, warm compresses, systemic antibiotics had to be stable within the last 30 days prior to Visit 1 and should be maintained stable throughout the study.

6.2 Prohibited Medications

Disallowed medications and treatments are listed in the Exclusion Criteria (Section 3.4). All medications and treatments that were not allowed prior to study are also not allowed during the study. No dry eye treatment such as artificial tears, gels, or ointments or True Tear™ device (Intranasal Tear Neurostimulator) shall be used within 24 hours prior to Visit 1 and through the whole duration of the study. Physical treatments such as lid scrubs, lid wipes, warm compresses and systemic antibiotics or oral supplements must be kept unchanged.

Specific prohibitions include:

- Topical steroids treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0
- [redacted]

6.3 Restrictions and Prohibitions

[redacted]

6.4 Examination Procedures

6.4.1 Procedures to be performed at each study visit with regard to study objective(s)

See Appendix 1 for a schedule of visits and measurements in recommended order. Appendix 3 describes the eye examinations. [redacted]

Visit 0 (Within 14 days before Visit 1): Screening

- Informed consent / HIPAA;
- Demographic data and medical / medication history;
- Review of inclusion / exclusion criteria;
- Adverse event query;
- Blood pressure and heart rate;
- Ocular Surface Disease Index (OSDI©) questionnaire;
- Visual acuity;
- Slit-lamp biomicroscopy;
- Tear Film Break-up Time (TFBUT);
- Fluorescein staining cornea (NEI grading);
- Lissamine green staining conjunctiva (Oxford scale);
- Meibomian gland assessment (MGD score);
- Schirmer's Test I (without anesthesia), [redacted]
- Intraocular pressure;
- Dilated fundoscopy;
- Blood sample collected for hematology and serum chemistry, and pregnancy test (if applicable);
- Qualified subjects will be scheduled for Visit 1.

Visit 1 (Day 1): Baseline/Randomization

- Medical/medication history update;
- Review of inclusion / exclusion criteria;
- Adverse event query;
- [redacted]
- Visual acuity;
- [redacted]
- Slit-lamp biomicroscopy;
- [redacted]
- Fluorescein staining cornea (NEI grading);
- [redacted]
- Randomization;
- In-office dose of study drug;
- Blood draw PK;
  - *Procedure at selected sites in a subset of subjects. Samples will be taken pre-dose and at 0.5, 1, 2, and 4 hours (±5 min for all time points) after instillation.
- Dispensation of diary and study drug for self-administered dosing until Visit 2;

- Subjects will be instructed about the frequency of dosing in each eye according to their assigned treatment;
- Subjects will be instructed to dose with study drug on the morning of their next visit [redacted]
- Subjects will record their symptoms on their diary each day prior to dosing with study drug;
- Subjects will indicate in the diary that their dose was taken, date and time, and number of drops;

Visit 2 (Day 15 ± 1): 2-Week Follow-Up

- In the beginning of the visit subject will be asked when he/she dosed with study drug and the time of the last dose before assessment will be collected. [redacted]
- Collection and review of study drug and diary;
- Medical/medication history update;
- Adverse event query;

[redacted]

- Visual acuity;

[redacted]

- Slit-lamp biomicroscopy;

[redacted]

- Fluorescein staining cornea (NEI grading);

[redacted]

- [redacted]
- Dispensation of diary and study drug for self-administered dosing until Visit 3;
  - Subjects will be instructed about the frequency of dosing in each eye according to their assigned treatment;
  - Subjects will be instructed to dose with study drug on the morning of their next visit [redacted]
  - Subjects will record their symptoms on their diary each day prior to dosing with study drug;
  - Subjects will indicate in the diary that their dose was taken, date and time, and number of drops

Visit 3 (Day 29 ± 2): 4-Week Follow-Up

- In the beginning of the visit subject will be asked when he/she dosed with study drug and the time of the last dose before assessment will be collected. [redacted]
- Collection and review of study drug and diary;
- Medical/medication history update;
- Adverse event query;
- [redacted]
- Visual acuity;
- [redacted]
- Slit-lamp biomicroscopy;

- [redacted]
- Fluorescein staining cornea (NEI grading);
- [redacted]
- [redacted]
- [redacted]
- Intraocular pressure;
- Dispensation of diary and study drug for self-administered dosing until Visit 4;
  - Subjects will be instructed about the frequency of dosing in each eye according to their assigned treatment;
  - Subjects will be instructed to dose with study drug on the morning of their next visit [redacted]
  - Subjects will record their symptoms on their diary each day prior to dosing with study drug;
  - Subjects will indicate in the diary that their dose was taken, date and time, and number of drops

Visit 4 (Day 57 ± 2):

- In the beginning of the visit subject will be asked when he/she dosed with study drug and the time of the last dose before assessment will be collected. [redacted]
- Collection and review of study drug and diary;
- Medical/medication history update;
- Adverse event query;
- Blood pressure and heart rate;
- [redacted]
- [redacted]
- [redacted]
- Visual acuity;

[redacted]

- Slit-lamp biomicroscopy;

[redacted]

- Fluorescein staining cornea (NEI grading);

[redacted]

- Intraocular pressure;
- Dilated fundoscopy;
- Blood sample collected for hematology and serum chemistry, and pregnancy test (if applicable);
- Blood draw PK (specific sites);
  - In the same subset of subjects at selected sites that participated in the Visit 1 PK draw.
  - 1 sample only at the end of the visit

6.4.2 Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 4 (Day 57 ± 2), then all safety evaluations should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

Adverse Events (both elicited and observed) and SAEs will be monitored throughout the study. The investigator will promptly review all AEs (both elicited and observed) for accuracy and completeness. All AEs will be documented on the appropriate source document and case report form.

If a female reports a pregnancy or has a positive pregnancy test during the study the investigator must report the pregnancy and the outcome of the pregnancy to [redacted] Product Safety within 24 hours of learning about the pregnancy.

A Pregnancy Questionnaire (provided in the Site Procedure Manual) will be completed by the study site's Principal Investigator. The Pregnancy Questionnaire will be sent to [redacted] Product Safety via the SAE Fax number[redacted]. The [redacted] Drug Safety Associate will forward the documentation to the Medical Monitor and the sponsor for review.

At the completion of the pregnancy, the Pregnancy Outcome form (provided in the Site Procedure Manual) is to be submitted to the [redacted]Product Safety Associate via the SAE fax number [redacted]. The [redacted] Product Safety Associate will manage the query and reconciliation process until the pregnancy documentation is complete.

6.4.3 Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Visual acuity;
- Slit-lamp biomicroscopy;
- Intraocular pressure;
- Dilated fundoscopy;
- Safety blood draws;
- Pregnancy test;
- PK samples (at selected sites)
- Assessment of AEs;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

6.4.4 Pharmacokinetic Samples

Samples for PK analysis will be collected at the scheduled time points (pre-dose and at 0.5, 1, 2, and 4 hours [±5 min for all time points] after instillation) at Visit 1. At Visit 4 and unscheduled visits, PK samples should only be taken once. The sample volumes are described in Section 9.8. Date and time of specified dose and date and actual PK sampling times will be recorded in the eCRF.

Samples will be processed, transferred to, and stored at the corresponding bioanalytical laboratory during the course of the study. This process will be detailed in a separate laboratory manual. After completion of the study, all samples will be destroyed after analysis or at the discretion of the sponsor.

6.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 0, 1, 2, and 3, and given written instructions (Appendix 2). The used and unused study drug bottles will be collected and counted at each visit from Visit 1 up to and including Visit 4 to assess dosing. 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. [redacted]

6.6 Subject Disposition

6.6.1 Completed Subjects

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

6.6.2 Discontinued subjects

Subjects may be discontinued prior to their completion of the study due to:

- Adverse events;
- Protocol violations;
- Administrative reasons (e.g. inability to continue, lost to follow up);
- Sponsor termination of study;
- Subject choice (e.g. withdrawal of consent);
- Other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the investigator.

Notification of a subject discontinuation and the reason for discontinuation will be made to the CRO and/or study sponsor and will be clearly documented on the eCRF.

Discontinued subjects will not be replaced.

6.7 Study 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 study drug, 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 investigational product.

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.

The whole trial may be terminated or suspended upon request of Health Authorities.

6.8 Study Duration

An individual subject's participation will involve 4 visits over approximately a 10-week period, including screening. After the study, subjects will be treated according to standard of care, as needed. The total duration of the study from first subject in to last subject out is expected to be 24 weeks (6 months).

6.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, subject safety, and ensure the study 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 study monitoring will be outlined in a monitoring plan.

Domestic and foreign regulatory agencies, [redacted] Product Safety (Clinical Research Organization [CRO]) 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 giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

7 ADVERSE EVENTS

7.1 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 (eg, an abnormal laboratory finding), symptom, or disease occurring after the subject signed Informed Consent Form (ICF) without any judgment about causality.

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

Worsening of Dry Eye Disease 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 decrease (defined as an increase of 0.22 or greater in logMAR score) from baseline (Visit 0) will be considered an Adverse Event.

Study drug includes the investigational drug under evaluation and any comparator drug, placebo, or any other medications required by the protocol given during any stage of the study.

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

7.1.1 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 patient/subject. The assessment of severity is made irrespective of relationship to study drug 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.

7.1.2 Relationship to Study Drug

The relationship of each AE to the investigational product 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 IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (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 study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

7.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drugs. 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 that is unrelated to the study drug.

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

7.2 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.

- 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 patient or 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.

7.3 Procedures for Reporting Serious Adverse Events

Using the SAE Report Form approved for this study, all SAEs and their outcomes must be reported to [redacted] Product Safety (who will notify the Medical Monitor and the study sponsor).

7.3.1 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the study drug, must be immediately (i.e. within a maximum 24 HOURS after becoming aware of the event) reported to [redacted] Product Safety. The [redacted] Product Safety Associate will forward the documentation to the Medical Monitor and the sponsor for review. Within 24 hours of knowledge of a new SAE, the investigator must enter the SAE information onto the hard copy SAE report form and transmit the form to the SAE Fax number below. The investigator must verify the report was received by [redacted]Product Safety. If the investigator is not able to successfully fax the SAE Report or verify it was successfully

received by [redacted] Product Safety, the investigator must call the [redacted] SAE Hot Line to report the SAE and follow-up with the [redacted] Product Safety Associate by phone [redacted] or email [redacted]

SAE Fax Number (US):[redacted]
[redacted]SAE Hot Line Number (US): [redacted]

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 study ID number
- Description of the Serious Adverse Event
- Date of the Serious Adverse Event
- Criterion for seriousness
- Preliminary assignment of causality to study drug

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 [redacted] Product Safety, [redacted] 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 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 [redacted] Product Safety and the study 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 study drug; and inform the IRB of the AE within their guidelines for reporting SAEs.

All SAEs will be reported from the start of the study product. All SAEs will be followed until resolution, stabilization, the event is otherwise, explained, or the subject is lost to follow-up.

7.3.2 Reporting a Suspected Unexpected Serious Adverse Reaction (SUSAR)

All SAEs that are 'suspected' (relationship to drug of definite, probable or possible) and 'unexpected' are to be reported to [redacted] Product Safety 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 (eg, United State Food and Drug Administration [FDA]) as required by the IRB/IEC, federal, state, and local regulations and timelines.

7.4 Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study 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 study treatment assignment from the Interactive Web Response System (IWRS). 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 7.3.1).

In a non-emergency situation, when a code break is required, it must be discussed with the Medical monitor and/or [redacted] Product Safety and the study 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 study and should complete both the Early Termination and Follow-up procedures.

Study staff will examine and reconcile study medication orders, records of receipts, dispensing records, and inventory forms throughout the study (see Section 9.5.2).

7.5 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 [redacted]Product Safety 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.

8 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

8.1 Analysis Populations

The following analysis populations will be considered:

- All Subjects – All subjects who sign the ICF

- Modified Intention-to-Treat – Modified Intention-to-Treat (mITT) includes all subjects randomly assigned to study treatment and who take at least 1 dose of study treatment. Subjects will be analyzed according to the treatment they are randomized to.

- Per Protocol Population – The Per Protocol (PP) population includes subjects in the safety population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

- Safety Population – The safety population includes all subjects who have received at least one dose of the investigational product. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

- PK Population – The PK population includes all subjects with an evaluable PK sample. The PK population will be used to summarize all perfluorohexyloctane blood concentrations.

The statistical analysis of safety data will be performed for the safety population. The analysis of efficacy data will primarily be performed for the mITT population. The efficacy analysis based on the PP population will serve as the sensitivity analyses.

8.2 Statistical Hypotheses

The following two sets of hypotheses will be tested as the primary hypotheses of the study:

H_{01}: The difference in the mean change from baseline to Week 8 total Corneal Fluorescein Staining (CFS) score between NOV03 QID and combined saline solution groups (NOV03 QID – combined saline solution) = 0 against

H_{11}: The difference in the mean change from baseline to Week 8 total CFS score between NOV03 QID and combined saline solution groups (NOV03 QID – combined saline solution) $\neq 0$

and

H_{02}: The difference in the mean change from baseline to Week 8 total CFS score between NOV03 BID and combined saline solution groups (NOV03 BID – combined saline solution) = 0 against

H_{12}: The difference in the mean change from baseline to Week 8 total CFS score between NOV03 BID and combined saline solution groups (NOV03 BID – combined saline solution) ≠ 0.

8.3 Sample Size

This study is expected to enroll 100 subjects in each of the four treatment arms, for a total of 300 randomized subjects. [redacted]

[redacted] this study has 88% power to detect a difference of 0.8 units in the change from baseline in corneal staining between an active arm and the combined control arm using a one-sided t-test at 5% level of significance. This assumes a standard deviation of 1.9 units for each arm.

8.4 Statistical Analysis

8.4.1 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, with placebo presented both pooled as well as separately for QID and BID dosing. 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 [redacted] will be one-sided at a significance level of 0.05.

8.4.2 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.

8.4.3 Missing Data

The primary efficacy analyses will be performed using the mITT population, and using a repeated measures model without any imputation for missing observations. Sensitivity analyses using different analysis populations and methods for handling missing data may be further detailed in the Statistical Analysis Plan (SAP).

[redacted]

8.4.4 Multiplicity Consideration

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

The hypothesis testing to compare the BID arm and control will only proceed if the QID vs. control comparisons are statistically significant.

8.4.5 Primary Efficacy Analyses

All efficacy analyses will be primarily based on the mITT. Population. Analyses based on Per-Protocol (PP) population will be supportive in nature. The primary evaluation of efficacy of the active arms will be against a combined control arm (with BID and QID saline solution). Analyses will also be provided comparing BID to QID saline solution to determine appropriateness of combining for the primary analysis. Sensitivity analysis may be undertaken for dosing-regimen matching control (that is, QID active vs. QID saline solution).

The primary analysis will be performed to compare the Week 8 difference in the change from baseline in total CFS between each of the active NOV03 groups and the combined saline solution group. The comparison will be conducted using a repeated measures model with treatment, site, visit, and treatment by visit interaction as fixed categorical factors, baseline as a continuous covariate, and using an unstructured covariance matrix. To establish evidence of efficacy in this proof of concept study, the hypothesis tests will be one-sided and performed at the 0.05 significance level.

The total CFS score is calculated as the sum of the staining from the inferior, central, superior, nasal, and temporal regions, such that a larger number indicates worse dry eye signs.

Treatment group contrasts and least-squared (LS) means will be presented from the model together with two-sided 95% confidence intervals.

The primary analysis will use the mITT population at the Visit 4, Week 8 visit; the PP population will also be used to further understand the primary results.

[redacted]

[redacted]

[redacted]

[redacted]

8.4.7 Safety Variables

All safety analyses will be performed on the Safety Population. The primary evaluation of safety of the active arms will be against a combined control arm (with BID and QID saline solution). The summaries of the safety data will be presented for a combined control arm as well as for each control arm separately. Additionally, the listings will have an indicator for subjects receiving BID or QID saline solution.

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 study drug discontinuation will also be summarized by treatment received.

Analysis of Adverse Events

Adverse events 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 study 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 and summarized by treatment group.

Analysis of Laboratory Parameters

Clinical laboratory parameters including hematology and serum chemistry will be summarized by treatment group and by visit. Baseline values, the values at each subsequent visit, and changes from baseline will be summarized for each of the quantitative laboratory assessments by treatment. Shift tables of chemistry and hematology, results will be used to summarize changes from baseline to study termination (or early termination). The number and percentage of chemistry and hematology values outside of normal ranges and/or with potential clinical importance will be summarized by visit and treatment.

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, safety laboratory, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.

8.4.8 Pharmacokinetic Variables

Whole blood for perfluorohexyloctane blood concentration measurements will be drawn from a minimum of 66 subjects at one or more investigational sites with the goal of having samples from 20 subjects per each of the active treatment arms. Blood concentrations of perfluorohexyloctane will be summarized descriptively. The following PK parameters will be estimated: $AUC_{0-\tau}$, C_{max}, t_{max}.

The relationship between safety endpoints and pharmacokinetic endpoints may be explored to understand the impact of PK parameters on safety.

Interim Analyses

No interim analyses are planned for this study.

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

This study 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 study drugs in the countries involved will be adhered to.

9.1 Protection of Human Subjects

9.1.1 Subject Informed Consent

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

All informed consent/assent forms must be approved for use by the sponsor and receive approval from an IRB/IEC prior to their use. If the consent form requires revision (eg, 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 study as well as those currently enrolled in the study.

9.1.2 Institutional Review Board (IRB) Approval

This study 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.

9.2 Ethical Conduct of the Study

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

9.3 Subject Confidentiality

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

Monitors, auditors and other authorized representatives of WCCT Product Safety, the sponsor, the IRB/IEC approving this study, 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 study subject's original medical and study 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 study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

9.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study 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 Case Report Forms serves as the investigator's record of a subject's study-related data.

9.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug 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 study drug. 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 study 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 study 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.

9.5 Labeling, Packaging, Accountability, and Return or Disposal of Study Drug

9.5.1 Labeling/Packaging

Investigational drug 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 5.4.1 for details regarding dispensation to subjects.

It should be noted that the pharmacist is also masked when dispensing study drug. The label will contain the following information:

As per the Code of Federal Regulations 21 part 312, section 312.6, the labels shall be comprised of:

- Protocol number
- Investigational new drug statement
- Lot number

- Storage conditions
- Name and address of the Sponsor

9.5.2 Accountability of Study Drug

The study drugs are only to be prescribed by the principal investigator or his/her named sub investigator(s), and are only to be used in accordance with this protocol. The study drugs must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drugs by maintaining a detailed inventory. This includes the amount of study drugs received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the sponsor upon the completion of the study

9.5.3 Return or Disposal of Study Drug

All study drugs will be returned to the sponsor or their designee for destruction.

9.6 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 transcribed to the eCRFs. The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study 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 (eg, by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff that have been trained on the system and have access to the system. Data will not be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each investigator site to be maintained on file by the investigator.

9.7 Publications

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

9.8 Handling of Biological Specimens

Blood samples will be collected for hematology (2 mL per draw), serum chemistry (5 mL per draw), pharmacokinetics (2 mL per draw), and pregnancy tests (if applicable, taken from 5 mL of serum). The approximate collection amounts per visit are described in Table 4:

Table 4. Blood Volumes for Safety Laboratory Tests and Pharmacokinetics

Approximate Blood Collection Amounts per Visit			
	Visit 0	Visit 1	Visit 4
Hematology	2mL	N/A	2mL
Serum Chemistry	5mL	N/A	5mL
PK	N/A	10mL	2mL
Total	**7mL**	**10mL**	**9mL**

- If blood samples are collected via an indwelling cannula, an appropriate amount (ie, 1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with saline or sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock.
- If subject is a female of childbearing potential, a serum pregnancy test will be taken.
- Pharmacokinetics testing for perfluorohexyloctane at selected sites only.

Clinical laboratory tests are listed in Table 5.

Table 5. Clinical Laboratory Tests

Hematology	Serum Chemistry	Pregnancy
Platelet count	Alanine aminotransferase (ALT)	Serum β- HCG
Red blood cell (RBC) count	Albumin	
Hemoglobin (Hb)	Alkaline phosphatase (ALP)	
Hematocrit (Hct)	Aspartate aminotransferase (AST)	
Mean cell volume (MCV)	Total bilirubin (T-Bil)	
Mean cell hemoglobin (MCH)	Blood urea nitrogen (BUN)	
Mean cell hemoglobin concentration (MCHC)	Calcium	
	Chloride	
Reticulocytes	Total cholesterol	
WBC count (with differential)	Creatinine	
Neutrophil	Creatine kinase (CK)	
Lymphocyte	Gamma-glutamyl transpeptidase (GGT)	
Monocyte	Total protein (TP) Albumin:Globulin ratio	
Eosinophil	Glucose	
Basophil	Lactic dehydrogenase (LDH)	
	Phosphorus	
	Sodium	
	Potassium	
	Magnesium	
	Total protein (TP)	
	Triglycerides	
	Uric acid	
	Bicarbonate	
	Globulin	
	low density lipoprotein (LDL)	
	high density lipoprotein (HDL)	

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