Clinical Trial Protocol

Protocol Title:	A Phase 3, Multi-Center, Open-Label Extension (OLE) Clinical Trial to Assess the Extended Long-Term Safety and Tolerability of NOV03 (Perfluorohexyloctane) in Subjects who Completed Trial NVU-003 (Kalahari OLE)
Protocol Number:	NVU-004
Trial Phase:	3
Investigational Product Name:	NOV03 (100% perfluorohexyloctane)
IND Number:	IND 130558
Indication:	Dry Eye Disease (*keratoconjunctivitis sicca*) associated with Meibomian Gland Dysfunction
Investigators:	Multi-Center
Sponsor:	Bausch & Lomb, Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807 USA
Clinical Research Organization:	Lexitas Pharma Services, Inc 313 Foster St. Durham, NC 27701 USA
IRB/IEC:	Sterling IRB 6300 Powers Ferry Rd Suite 600-351 Atlanta, GA 30339
Version:	3.0
Amendment 2	12 MAR 2020
Amendment 1	13 DEC 2019
Original Protocol Date:	14 OCT 2019

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

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1.2 SYNOPSIS

Protocol Title:	A Phase 3, Multi-Center, Open-Label Extension (OLE) Clinical Trial to Assess the Extended Long-Term Safety and Tolerability of NOV03 (Perfluorohexyloctane) in Subjects who Completed Trial NVU-003 (Kalahari OLE)
Protocol Number:	NVU-004
Investigational Medicinal Product:	NOV03 (100% perfluorohexyloctane)
Trial Phase:	3
Trial Objective:	The primary objectives of this trial are to evaluate the safety and tolerability of perfluorohexyloctane (NOV03) ophthalmic solution during long-term use in subjects with Dry Eye Disease (DED) associated with MGD (Meibomian Gland Dysfunction). The other objective is to evaluate the efficacy of perfluorohexyloctane (NOV03) solution during long-term use in subjects with DED associated with MGD.
Overall Trial Design	
Structure:	Open-label, multicenter, single-arm
Participant Duration:	Approximately 52 weeks.
Trial Duration:	The estimated trial duration is 18 months, from first subject first visit (FSFV) until last subject last visit (LSLV).
Dosage/Dose Regimen:	Subjects who completed trial NVU-003 and meet all of the inclusion and none of the exclusion criteria will receive the following bilateral ophthalmologic treatment beginning with Visit 1 and ending with Visit 6. 1) NOV03 (100% perfluorohexyloctane) 4 times daily (QID).
Summary of Visit Schedule:	6 visits over the course of approximately 52 weeks • Visit 1 = Day 1, open label treatment start (= Day 57 of NVU-003 trial) • Visit 2 = week 4 ± 2 days, • Visit 3 = week 12 ± 7 days, • Visit 4 = week 26 ± 7 days, • Visit 5 = week 40 ± 7 days, • Visit 6= week 52 ± 7 days

	7 telephone calls (TC; optionally onsite visits) • TC 1= week 8 follow-up ± 2 days • TC 2 = week 16 follow-up ± 7 days • TC 3 = week 22 follow-up ± 7 days • TC 4 = week 30 follow-up ± 7 days • TC 5 = week 36 follow-up ± 7 days • TC 6 = week 44 follow-up ± 7 days • TC 7 = week 48 follow-up ± 7 days
Measures Taken to Reduce Bias:	• Subjects shall be instructed not to discuss investigational medicinal product (IMP) characteristics and/or their experience with the IMP with other trial participants. • Follow-up NVU-004 subject visits should not be scheduled for the same day as NVU-003 subject visits at a given site to prevent unblinding of NVU-003. • If NVU-003 and NVU-004 subjects are present at the clinical site at the same time, the site should take precautions to prevent subjects from interacting.
Trial Population Characteristics	
Number of Subjects:	Approximately 200 subjects who completed trial NVU-003 will be enrolled at up to 20 clinical sites.
Condition/Disease:	Dry Eye Disease (*keratoconjunctivitis sicca*) associated with Meibomian Gland Dysfunction
Inclusion Criteria:	**Subjects must:** 1. Have completed trial NVU-003 without major protocol deviations, and have been compliant with NVU-003 trial procedures and application of IMP. 2. Have a subject reported history of DED in both eyes for at least 6 months prior to Visit 0 of NVU-003 and be diagnosed with DED at Visit 1 of NVU-003. 3. Provide written informed consent. 4. Be able and willing to follow instructions, including participation in all trial assessments and visits.
Exclusion Criteria:	**Subjects must not:** 1. Have permanently discontinued IMP during NVU-003 for any reason. 2. Have any clinically significant ocular surface slit-lamp findings at Visit 1 and/or in the opinion

	of the investigator have any findings that may interfere with trial parameters. 3. Have an ocular or periocular malignancy. 4. Have a history of herpetic keratitis. 5. Have any planned ocular and/or lid surgeries over the trial period. 6. Be a woman who is pregnant or planning a pregnancy. 7. Be unwilling to submit to a urine pregnancy test at Visit 2, 3, 4, 5 and Visit 6 (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). 8. 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. 9. Have a known allergy and/or sensitivity to the IMP. 10. Be currently enrolled in an investigational drug or device trial other than NVU-003 or NVU-004. 11. Have 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 1. 12. Have a condition or be in a situation 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.
Trial Formulations:	• 100% Perfluorohexyloctane
<u>Evaluation Criteria</u>	

Efficacy and Safety Endpoint(s):	**Primary Safety Endpoints:** 1. Ocular and non-ocular adverse events **Secondary Safety Endpoints:** 1. Visual acuity (BCVA using ETDRS) 2. Slit-Lamp biomicroscopy 3. Intraocular pressure 4. Dilated fundoscopy **Other Pre-specified Efficacy Endpoints:** 1. CFB of Dryness Score (VAS) to each measured post-baseline visit. 2. CFB in tCFS (NEI scale) to each measured post-baseline visit. 3. CFB in CFS sub-regions (NEI scale) to each measured post-baseline visit. 4. Proportion of tCFS responders (≥3 improvement based on NEI scale) at each measured post-baseline visit. 5. Proportion of Dryness Score responders (≥30 % improvement from baseline) at each measured post-baseline visit. 6. Proportion of cCFS responders (≥1 improvement based on NEI scale) at each measured post-baseline visit. 7. CFB in Visual Analogue Scale (VAS) burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms (VAS) at each measured post-baseline visit. 8. CFB in Ocular Surface Disease Index (OSDI©) at each measured post-baseline visit.
Exploratory Endpoints:	1. Meibomian Gland Assessment (MGD score) at each measured post-baseline visit. 2. Schirmer's Test I (without anesthesia) at each measured post-baseline visit. 3. TFBUT at each measured post-baseline visit.
Other	Eyedrop Comfort and Acceptability Questionnaire
General Statistical Methods and Types of Analyses <u>Sample Size</u> Approximately 200 subjects will be enrolled in order to ensure that at least 100 evaluable subjects complete the week 26 (6 month) treatment period and at least 100 evaluable subjects complete the week 52 (12 month) treatment period.	

With 100 subjects completing the week 52 (or week 26) treatment period, the study will have 95% or greater chance of observing adverse events that occur at a true incident rate of 3.0% or higher.

Primary Safety Analyses

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 as received in NVU-003 and overall. An AE is treatment emergent if it occurs or worsens after first dose of trial treatment in NVU-004.

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 provided for ocular and non-ocular AEs. Ocular AEs will be summarized at the subject level, at the eye level, and separately for study and fellow eyes.

Secondary Safety Analyses

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by visit using descriptive statistics by treatment group as assigned in NVU-003 and overall. For assessments performed by eye, study eye and fellow eye will be summarized separately. Changes or shifts from baseline (baseline as defined in NVU-003) will be summarized where appropriate.

Further Analyses

Quantitative other pre-specified efficacy endpoints will be summarized descriptively (n, mean, standard deviation, median, min and max) by visit and treatments group as assigned in NVU-003 and overall. Changes from baseline (as defined in NVU-003) will also be summarized. Assessments performed by eye, study eye and fellow eye will be summarized separately.

Dichotomous other pre-specified efficacy endpoints will be summarized descriptively (frequency and percentage).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BCVA	Best-corrected Visual Acuity
BID	Two times daily
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
cCFS	Central Corneal Fluorescein Staining
CFB	Change from Baseline
CFR	Code of Federal Regulations
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
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
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
NDA	New Drug Application
NEI	National Eye Institute
NOV03	100% perfluorohexyloctane
OD	right eye
OLE	Open label extension
OS	left eye

OSDI©	Ocular Surface Disease Index
OSI	Objective Scattering 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 Event
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 (Schiffmann 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 associated with MGD.

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. In addition, NOV03 penetrates into the meibomian glands, where it potentially interacts with and dissolves the altered, viscous meibum secretion in the glands. 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 Post Market Clinical Follow-up studies NT- 001, NT- 002, NT- 003 and NT- 004 with the perfluorohexyloctane containing medical device (NovaTears®), which showed that subjects with evaporative DED and MGD benefitted most. Clinical data from observational studies NT- 001 and NT- 002 consistently indicate that NOV03 is efficacious in treating signs and symptoms of mild to moderate evaporative DED and mild to moderate DED associated with MGD. Clinical study NT- 004 demonstrated that NOV03 increases tear film thickness (TFT) and lipid layer thickness (LLT) compared to saline solution and therefore provides further clinical evidence supportive for the use of NOV03 for evaporative forms of DED.

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

For the US development of NOV03, a phase 2 trial NVU-002 (SEECASE-1) was conducted. NVU-002 was a randomized, double-masked, saline-controlled trial to evaluate the effect of NOV03 at two different dosing regimens (QID and BID) on signs and symptoms of DED after 8 weeks treatment duration.

The trial showed efficacy of NOV03 in sign and symptom outcomes, in a highly symptomatic predominantly evaporative DED population with clinically significant MGD presence. It met its prespecified primary efficacy endpoint of superior change from baseline in tCFS at week 8 for both BID and QID dosing regimens compared to the combined saline control with high statistical significance. NOV03 showed clinically meaningful improvements in a variety of symptoms. The effects on Dryness Score, awareness of DED symptoms, and frequency of dryness were highly statistically significant over the combined dosing regimens of the saline control. Benefits in both signs and symptoms were dose-schedule-dependent favoring the QID schedule over the BID schedule. The treatment effects started early (2 weeks) and were maintained throughout the visits. NOV03 was safe and well tolerated after 8 weeks of BID or QID dosing. Results are planned to be confirmed in the pivotal trial NVU-003 (SEECASE-2), a randomized, double-masked, saline-controlled trial to evaluate the effect of NOV03 on signs and symptoms of Dry Eye Disease associated with Meibomian Gland Dysfunction.

Subjects successfully completing NVU-003 will be offered to continue treatment in the phase 3, open-label extension trial NVU-004 (Kalahari OLE). NVU-004 is designed to gain information on long-term safety and tolerability of NOV03 QID dosing of subjects completing the 8-weeks treatment in trial NVU-003.

3 TRIAL OBJECTIVES

3.1 Primary Objective

- The primary objective of this trial is to evaluate the safety and tolerability of NOV03 (perfluorohexyloctane) ophthalmic solution during long-term use in subjects with Dry Eye Disease associated with MGD.

3.2 Secondary Objectives

- The secondary objective is to evaluate the efficacy of NOV03 (perfluorohexyloctane) solution during long-term use in subjects with Dry Eye Disease associated with MGD.

4 TRIAL DESIGN

4.1 Overall Trial Design

This is a phase 3, multicenter, open-label, single-arm extension clinical trial to assess the extended long-term safety and tolerability of NOV03 (100% perfluorohexyloctane) at a QID dosing regimen. Approximately 200 subjects who completed the clinical trial NVU-003 and meet all other NVU-004 trial eligibility criteria will be included at approximately 20 clinical sites in the US to receive treatment with NOV03.

NVU-004 eligible subjects will dose the IMP (NOV03) ophthalmologically and bilaterally QID for approximately 52 weeks.

4.2 End of Trial Definition

The end of the trial for an individual subject is defined as that subject's last 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 (Appendix 1) for all subjects in the trial.

4.3 Visit Description and Telephone Calls

Subjects will be required to sign an Informed Consent before completing any NVU-004 trial related procedure. All trial procedures are listed in Section 8.4 and in the schedule of assessments 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 shall be instructed not to discuss IMP characteristics and/or their experience with the IMP with other subjects during each visit.

Follow-up NVU-004 subject visits should not be scheduled for the same day as any NVU-003 subject visits at a given site to prevent unblinding of NVU-003.

If NVU-003 and NVU-004 subjects are present at the clinical site the same time, the site should take precautions to prevent subjects from interacting.

Day 1 (Visit 1)

The results of assessments at Visit 4 (Day 57) in study NVU-003 (=final visit) will be taken as Day 1 data for NVU-004. Further data/assessments to be captured will be the NVU-004 Informed Consent, Inclusion/Exclusion Criteria to determine NVU-004 eligibility, Non-leading Adverse Event questioning (AE query) and IMP dispensation.

Subjects will be given a 4-bottle IMP supply and will self-administer a single drop of the trial medication into both eyes at the clinic. Each subject will be given a dosing diary to record the number of IMP doses taken daily. Study staff will remind the subject how to use the dosing diary and when the remaining doses should be taken.

Visits 2-6 / (ET)

Subjects will return to the clinic on week 4±2 days (Visit 2), week 12±7 days (Visit 3), week 26±7 days (Visit 4), week 40 ±7 days (Visit 5), week 52±7 days (Visit 6/Early Termination (ET)) to be evaluated for ocular and non-ocular adverse events and signs and symptoms of DED. IMP and the subject diary will be collected and reviewed. All used and unused trial medication should be returned to the clinic and a new trial medication kit will be dispensed.

The subject will be asked to complete an eyedrop comfort and acceptability questionnaire during Visit 6/ET. Subjects will be discharged from the trial after all Visit 6/ET assessments have been completed.

Telephone Calls (TC)

Seven (7) telephone calls are scheduled at week 8±2 days (TC 1), week 16 ±7 days (TC 2), week 22 ±7 days (TC 3), week 30 ±7 days (TC 4), week 36 ±7 days (TC 5), week 44 ±7 days (TC 6), week 48 ±7 days (TC 7). During each telephone call the subjects will be interviewed using non-leading AE questioning and asked for medical and/or concomitant medication updates.

Early Termination

Subjects who terminate early during the treatment period will be asked to complete all assessments as indicated at Visit 6 on the schedule of assessments prior to commencement of any alternative DED therapy (if considered possible). Dosing diary and trial medication will be collected. Subjects who are terminated early from the trial will not be replaced.

4.4 Trial Flow

All subjects will be expected to progress from Visit 1 through trial exit at Visit 6 (week 52). All subjects will follow the trial structure with visits and telephone-calls (TC) as shown in Figure 1. Most Visit 1 assessments are the same assessments from Visit 4 in NVU-003. The detailed assessments are depicted in the schedule of assessment in Appendix 1.

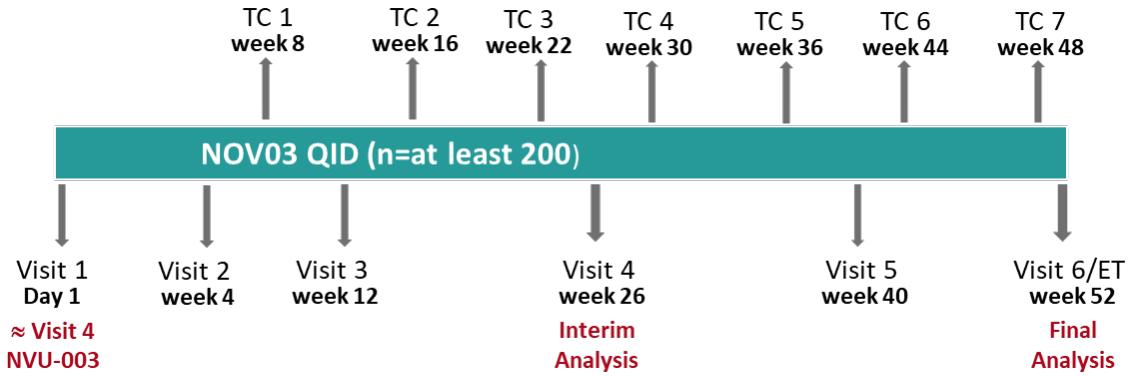

Figure 1 NVU-004 Trial Flow Chart

4.5 Enrollment and Treatment Assignment

Subjects will keep the assigned unique subject number as allocated in clinical trial NVU-003. If all inclusion and exclusion criteria are met at Visit 1, the first approximately 200 qualifying subjects will be included in NVU-004. IRS will be used to assign drug kit numbers at visits 1, 3, 4 and 5.

Each subject will spend approximately 52 weeks in the trial. The total duration of the trial from First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV) is expected to be approximately 18 months.

4.6 Justification of Trial Design

This 52-week open-label extension trial will enroll subjects successfully completing trial NVU-003. The open-label single-arm treatment design is deemed adequate for investigating long-term safety/tolerability of NOV03 QID at regular intervals in at least 100 subjects in long term (52-week), day to day use. An interim analysis will be performed after 100 subjects complete 26-weeks of treatment.

4.7 Justification of Dose

NOV03 has demonstrated efficacy for signs and symptoms of DED in the phase 2 trial NVU-002 at two NOV03 dosing regimens (QID and BID) versus saline. In NVU-002 the NOV03 QID regimen showed more pronounced effects for several efficacy parameters

compared to the NOV03 BID and saline regimens. Therefore, the NOV03 QID regimen was chosen for the phase 3 trial NVU-003 to replicate the 8-weeks efficacy and safety results of NVU-002. No safety and tolerability issues were observed in the 8 weeks NVU-002 trial with this treatment schedule. Therefore, the open label extension trial NVU-004 will use the same NOV03 dose schedule used in NVU-003.

5 TRIAL POPULATION

5.1 Number of Subjects (approximate)

Approximately 200 subjects who completed the clinical trial NVU-003 will be enrolled at approximately 20 sites to achieve at least 100 subjects completing 26 weeks and 52 weeks dosing with respective safety and tolerability assessments.

5.2 Trial population characteristics

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

Subjects who completed trial NVU-003 without major protocol deviations, have been compliant with NVU-003 trial procedures and application of IMP may be invited to enroll into trial NVU-004.

5.3 Inclusion Criteria

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

1. Have completed trial NVU-003 without major protocol deviations, and have been compliant with NVU-003 trial procedures and application of IMP.
2. Have a subject reported history of DED in both eyes for at least 6 months prior to Visit 0 of NVU-003 and be diagnosed with DED at Visit 1 of NVU-003.
3. Provide written informed consent.
4. 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**:**

Subjects must not:

1. Have permanently discontinued investigational medicinal product during NVU- 003 for any reason.

2. Have any clinically significant slit-lamp findings or ocular condition at Visit 1 and/or in the opinion of the investigator have any findings that may interfere with trial parameters.
3. Have an ocular or periocular malignancy.
4. Have a history of herpetic keratitis.
5. Have any planned ocular and/or lid surgeries over the trial period.
6. Be a woman who is pregnant or planning a pregnancy.
7. Be unwilling to submit to a urine pregnancy test at Visit 2, 3, 4, 5 and Visit 6 (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).
8. 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.
9. Have a known allergy and/or sensitivity to the investigational medicinal product (IMP).
10. Be currently enrolled in an investigational drug or device trial other than NVU-003 and NVU-004.
11. Have 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 1.
12. Have a condition or be in a situation 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.

5.5 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 from the trial for any of the following reasons:

- 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 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 subject`s consent.

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, the sponsor/sponsor designee 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 Primary Endpoints

Ocular and non-ocular AEs

6.2 Secondary Endpoints

Safety Endpoints:

1. Visual acuity (BCVA using ETDRS)
2. Slit-Lamp biomicroscopy
3. Intraocular pressure
4. Dilated fundoscopy

Other Pre-specified Efficacy Endpoints:

1. CFB of Dryness Score (VAS) to each measured post-baseline visit.
2. CFB in tCFS (NEI scale) to each measured post-baseline visit.
3. CFB in CFS sub-regions (NEI scale) to each measured post-baseline visit.
4. Proportion of tCFS responders (≥3 improvement based on NEI scale) at each measured post-baseline visit.
5. Proportion of Dryness Score responders (≥30 % improvement from baseline) at each measured post-baseline visit.
6. Proportion of cCFS responders (≥1 improvement based on NEI scale) at each measured post-baseline visit.

7. 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 (VAS) at each measured post-baseline visit.
8. CFB in Ocular Surface Disease Index (OSDI©) at each measured post-baseline visit.

6.3 Exploratory Endpoints

1. Meibomian Gland Assessment (MGD score) at each measured post-baseline visit.
2. Schirmer's Test I (without anesthesia) at each measured post-baseline visit.
3. TFBUT at each measured post-baseline visit.

6.4 Other Endpoints

In addition to the safety and efficacy endpoints above, the comfort and acceptability of the trial drug will be assessed using an Eyedrop Comfort and Acceptability Questionnaire.

7 TRIAL MATERIALS

7.1 Investigational Medicinal Product

7.1.1 IMP(s)/ Formulation

NOV03 drug product is a thin clear, preservative-free ophthalmic solution drop (see Table 1).

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
Manufacturer:	Alliance Medical Products, Inc., DBA Siegfried Irvine, 9342 Jeronimo Rd., Irvine, CA 92618, USA

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 4 bottles of NOV03. 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 are 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 (at each clinical site) and must not be refrigerated.
Subjects should be instructed to store IMP at room temperature and out of children's reach at all times. Subjects should not use a dispensed bottle that has been opened for more than 30 days.

7.1.4 IMP Dispensation

- At the end of Visit 1, qualified subjects will be enrolled and the investigator, or designee will dispense the subject one kit of IMP containing 4 individual bottles.
- One kit will be dispensed per treatment period. The first dose of NVU-004 Study IMP will be administered at the clinical site.
- At Visit 2, IMP will not be dispensed. In case the subject wants to withdraw from the trial during this visit, the kit should be returned.
- At Visits 3, 4 and 5 subjects will receive a new kit of IMP.
- At Visits 3, 4, 5 and 6 used/unused IMP will be collected from subjects for drug accountability.

Subjects will be instructed to immediately contact the site if there is any problem with the IMP, e.g. kit/bottle(s) was damaged or lost or if the open bottle was dropped. In case the 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.

7.1.5 Instructions for Use and Administration

At Visit 1 subjects will be instructed by the site`s staff on appropriate hygiene and eye drop dosing technique for multiple use drops. At Visit 1, subjects will self-administer in the clinic NOV03 eye drops in each lower cul-de-sac of each eye under the supervision of the site staff as shown in Appendix 2.

Subsequent eye drops are to be instilled by the subjects according to detailed written instructions.

Subjects will be instructed to instill their drops in both eyes QID for the duration of the trial. Clinic staff will instruct the subjects to dose at approximately the same time every day e.g. morning, lunch time/midday, afternoon/early evening, and at bedtime. If a dose is missed, then the next dose should be administered on time.

Subjects will be informed on how to store (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 IMP bottles are designed for multiple use. Subjects will be instructed to only open one bottle at a time. They should be instructed not to discard the empty bottles but keep them in the kit box and return them at their next visit in the kit box.

Subjects will record in their dosing diary that their doses were taken.

7.2 IMP Accountability

The investigator or designated site personnel 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 designated site personnel. 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 designated site personnel. 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 used 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 disposal facility prior to full accountability by sponsor's monitor.

7.3 IMP Handling and Disposal

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 disposal facility 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 provide a copy of all completed drug disposition forms to the sponsor after the completion of the trial.

7.4 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 the manual of operations.

8 TRIAL METHODS AND PROCEDURES

8.1 Concurrent Medications and Therapies

The use of any concurrent medication/therapy, 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.

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. 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.

Starting with Visit 2, Artificial tears (preferably preservative free) may be used, their use needs to be documented. The use of treatments for DED such as gels, ointments, TrueTear™ device (Intranasal Tear Neurostimulator), are allowed after an unsuccessful trial of artificial tears.

In case clinical judgment considers it necessary, treatment with topical steroids or other topical prescription medications are allowed according to clinicians' prescription. Their use will be documented in the subject's source document and corresponding eCRF.

Changes in physical ocular therapies such as lid scrubs, lid wipes, warm compresses should be recorded on the subject's source document and corresponding eCRF.

8.2 Prohibited Medications/ Treatments

Wearing of contact lenses and ocular surgery/ocular laser treatment of any kind is not allowed. In case ocular surgery becomes necessary during the trial the medical monitor should be contacted regarding further NOV03 treatment continuation. LipiFlow procedure or any kind of other procedures affecting meibomian glands during the trial is not allowed. Concurrent enrollment in another investigational drug or medical device trial is not permitted.

8.3 Restrictions and Prohibitions

Subjects will be asked to refrain from the following, for **24 hours** prior to their visits:

- Dangerous sport activities (e.g. skiing, mountain climbing, etc.).
- Challenging climates (e.g. smoking rooms, sauna, airplane etc.).

Subjects will be asked to refrain from the following for **12 hours** prior to their visits:

- Swimming in a chlorinated pool.

In case visual disturbances should occur upon instillation of the drop the subject is advised not to drive or use machinery until such effects have disappeared.

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. Subjects shall bring their trial medication to each visit.

Visit 1 (Day 1)

Note: Assessments from NVU-003 are depicted in *italics.*

- Informed consent / HIPAA
- *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;*
- *Medical/Surgical History* (see Section 9.1 on how to record medical history and ongoing AEs);
- *Demographics (from V0 in NVU-003);*
- *Previous/Concomitant Medication (from V4 in NVU-003);*
- Review of inclusion / exclusion criteria;
- *Urine Pregnancy test (from V4 in NVU-003);*
- *Dryness Score (VAS Severity of Dryness) (from V4 in NVU-003);*
- *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 (from V4 in NVU-003);*
- *Ocular Surface Disease Index (OSDI©) questionnaire (from V4 in NVU-003);*
- *Visual acuity (ETDRS) (from V4 in NVU-003);*
- *Slit-Lamp biomicroscopy (from V4 in NVU-003);*
- *Tear Film Break-up Time (TFBUT) (from V4 in NVU-003);*
- *Fluorescein staining (NEI scale) (from V4 in NVU-003);*
- *Meibomian gland assessment (MGD score) (from V4 in NVU-003)* (wait 5 min before start of Schirmer`s Test);
- *Schirmer's Test I (without anesthesia) (from V4 in NVU-003);*
- *Intraocular Pressure (from V4 in NVU-003);*
- *Dilated Fundoscopy (from V4 in NVU-003);*
- Non-leading AE questioning (Adverse event query);
- In-office dose of IMP;
- Dispensation of dosing diary and IMP for self-administered dosing until Visit 3;
  - Subjects will be instructed how to administer IMP;
  - Subjects will be instructed to dose with IMP on the morning of their next visit at least 2 hours before the start of their visit (Visit 2);
  - Subjects will be instructed on how to fill the dosing diary.
- Dispensation of one IMP kit;
- Subjects are scheduled for Visit 2

Visit 2 (week 4 ± 2 days), Visit 3 (week 12 ± 7 days), Visit 4 (week 26 ± 7 days), Visit 5 (week 40 ± 7 days):

- 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
  - Ask subject if he/she dosed with IMP the morning of Visit 2 and, if applicable, record the time of the dose
- Concomitant Medication update;
- Urine Pregnancy Test (as needed)
- 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) (at Visit 4);
- Intraocular Pressure;
- Dilated Fundoscopy (at Visits 3, 4, 5);
- Non-leading AE questioning (Adverse event query);
- Dispensation of dosing diary;
  - Subjects will be instructed how to administer IMP;
  - Subjects will be instructed to dose with IMP on the morning of their next visit at least 2 hours before the start of their visit ;
  - Subjects will be instructed on how to fill the dosing diary.
- Drug Dispensation of one kit (at Visits 3, 4, 5);
- Subjects are scheduled for the next Visit

Visit 6 (week 52± 7 days) 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 dosing 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 Comfort and 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.

TC 1-7 (Weeks 8/ 16/ 22/ 30/ 36/ 44/ 48 ± 7 days)

- Medical/Concomitant Medication Update
- Recording of Adverse Events (see also Section 9.1)

8.4.2 Early Termination/Discontinuation

Data from subjects discontinuing after randomization will be captured completely in the eCRF including Early Termination Visit and reason for discontinuation. If a dosed subject is discontinued from the trial prior to Visit 6 (week 52), then all evaluations planned for Visit 6 (week 52) should be performed on the day of discontinuation (early termination visit) or at the discretion of the investigator.

8.4.3 Unscheduled Visits

An unscheduled visit may be performed during the course of the trial 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 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, 3, 4 and 5 and provided with written instructions (Appendix 2). Subject diaries and IMP (used and unused bottles) will be collected from subjects at each visit from Visit 2 up to and including Visit 6 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.

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;
- Lack of efficacy;
- Withdrawal by subject;
- Protocol violation;
- Lost to follow up;
- Sponsor termination of trial;
- Death
- Other

Subjects must be discontinued as outlined in Section 5.5.

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 6 visits over approximately a 52-week period. 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 FSFV until LSLV is expected to be 18 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.

AEs ongoing at the time of Visit 4 (Day 57) in trial NVU-003 and prior to IMP administration at Visit 1 of NVU-004 will not be considered an AE for NVU-004. These will be recorded as medical history in NVU-004. If there is a worsening of such medical history after administration of the IMP, this should be considered a new AE and reported.

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 in NVU-004 (defined as an increase of 0.22 or greater in logMAR score) from Visit 0 in NVU-003 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) 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.

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 an 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.

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 Adverse Events and 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 Drug Safety Navigator (who will notify the medical monitor and the trial sponsor). All information relevant to the SAE must be recorded on the appropriate SAE report form. The CRO Drug Safety Navigator 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 CRO Drug Safety Navigator. If the investigator is not able to successfully fax the SAE Report or verify it was successfully received by CRO Drug Safety Navigator, the investigator must call the CRO SAE Hot Line to report the SAE and follow-up with the CRO Drug Safety Navigator Associate by phone (**see phone/fax numbers and email in safety management plan (SMP)**).

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 Drug Safety Navigator, 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 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 Drug Safety Navigator 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 as of the signature of Informed Consent. All SAEs will be followed until resolution, stabilization, the event is otherwise, explained, or the subject is lost to follow-up.

9.3.2 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 CRO Drug Safety Navigator 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 unmasked as this is a single-arm and open label extension trial.

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 Drug Safety Navigator 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 subject should be discontinued from the study and the investigator must report the pregnancy and the outcome of the pregnancy to the CRO Drug Safety Navigator Associate within 24 hours of learning about the pregnancy.

A Pregnancy Reporting Form will be completed by the trial site's principal investigator and sent to CRO Drug Safety Navigator (*see **SMP***). The CRO Drug Safety Navigator will forward the documentation to the medical monitor and the sponsor for review.

At the completion of the pregnancy, the Pregnancy Outcome Form is to be submitted to the CRO Drug Safety Navigator via the SAE contact details. The CRO Drug Safety Navigator will manage the query and reconciliation process until the pregnancy documentation is complete.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

Safety Set (SAF) – The SAF includes all enrolled subjects who have received at least one dose of the investigational product in this study. The SAF will be analyzed for all assessments. Subjects in the SAF will be analyzed as treated.

The statistical analysis of baseline, and primary/secondary endpoint data will be performed for the SAF.

Data will be summarized by treatment group as received in NVU-003 and overall. Group 1 and group 2 consist of subsets of subjects who received masked treatment with NOV03 or saline, respectively, in NVU-003.

10.2 Statistical Hypotheses

There are no formal hypotheses to be tested in this open-label safety extension trial.

10.3 Sample Size

Approximately 200 subjects will be enrolled in order to ensure that at least 100 evaluable subjects complete the week 26 treatment period and at least 100 evaluable subjects complete the week 52 treatment period.

With 100 subjects completing the week 52 (or week 26) treatment period, the study will have 95% or greater chance of observing adverse events that occur at a true incident rate of 3.0% or higher.

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. Qualitative variables will be summarized using counts and percentages.

Summaries will be provided for demographics, 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.

Presentation will be by treatment group for subjects treated with NOV03 in NVU-003 and subjects treated with the saline comparator in NVU-003 as well as overall.

The results of assessments performed at multiple visits will be presented by visit as appropriate unless otherwise specified.

The results of bilateral ocular assessments will be summarized separately for study and fellow eyes.

Baseline measures are defined as the measure prior to the administration of IMP in the double masked trial NVU-003, e.g. baseline in NVU-003 and NVU-004 are identical. CFB will be calculated as Value at Follow-up Visit – Value at Baseline Visit.

10.4.2 Unit of Analysis

For efficacy endpoints, the unit of analysis will be the study eye which was determined during NVU-003. This information will be transferred to this NVU-004 trial.

10.4.3 Missing Data

The primary analysis will be completed on the SAF with available data per subject.

10.4.4 Multiplicity Considerations

This section is not applicable.

10.4.5 Primary Safety Analyses

All safety analyses will be performed on the Safety Population.

Dosing information will be summarized overall and by treatment from NVU-003 and listed for each subject. Discontinuation of treatment will be summarized. The primary reason for IMP discontinuation will also be summarized by treatment group as received in NVU-003. Adverse events (AEs) will be coded using the MedDRA dictionary. An AE will be defined as treatment emergent if it occurs or worsens after the first dose of trial treatment in clinical trial NVU-004.

Frequencies and percentages of subjects with TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided. 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 provided for ocular and non-ocular AEs. Ocular AEs will be summarized at the subject level, at the eye level, and separately for study and fellow eyes.

The treatment groups as assigned in NVU-003 will be compared descriptively with regard to safety endpoints. No inferential comparison will be conducted.

Concomitant medications will be coded using the most recent version of WHO-Drug Dictionary.

10.4.6 Secondary Safety Analyses

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by visit and by treatment group as received in NVU-003 using descriptive statistics. Changes from baseline (baseline as defined in clinical trial NVU-003) will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

10.4.7 Other Pre-specified Efficacy Analyses

The analysis of other pre-specified efficacy endpoints will use the SAF with available data per subject.

Quantitative other pre-specified efficacy endpoints will be summarized descriptively (n, mean, standard deviation, median, min, and max) by visit and by treatment group as assigned in NVU-003.

Dichotomous other pre-specified efficacy endpoints will be summarized descriptively (frequency and percentage).

10.4.8 Exploratory Analyses

Exploratory endpoints MGD score, Schirmer`s Test I, and TFBUT will be summarized descriptively.

10.4.9 Ocular Comfort and Acceptability Analyses

Eyedrop comfort and acceptability will be assessed on the SAF population with available data per subject. The data will be summarized descriptively.

10.4.10 Interim Analyses

An interim safety analysis is planned for the first 100 subjects completing 26 weeks treatment with IMP including all assessments of Visit 4. This 26-week interim report will be used to submit the initial NDA. The safety analyses will be identical to the final analyses after 52 weeks of treatment with IMP including Visit 6 (52 weeks).

10.5 Additional Analyses

Additional analysis of study measures, combining / pooling data with trial NVU-003 and / or NVU-002 might be described in a statistical analysis plan, separate from the formal study statistical analysis plans.

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/assent 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/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 (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.

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 Drug Safety Navigator, 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 transcribed to the eCRFs. The investigator is responsible for ensuring that trial data is completely and accurately recorded on each subject's eCRF, source documents, 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). 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 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. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the trial 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.

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, CRO Drug Safety Navigator 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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3. Le Q, Zhou X, Ge L, Wu L, Hong J, Xu J. (2012). Impact of dry eye syndrome on vision-related quality of life in a non-clinic-based general population. BMC Ophthalmology ; 12(22): 1-8.
4. Lemp M. (1995). Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes. *CLAO J.*; 21 (4): 221-32.
5. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. (2003). Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Trial. Ophthalmology ; 110(6):1096-101.
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8. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. (2003). Prevalence of dry eye syndrome among US women. Am J Ophthalmol, 136, 318-26.
9. Schaumberg DA, Dana R, Buring JE, Sullivan DA (2009). Prevalence of dry eye disease among US men: estimates from the Physician's Health Studies. Arch Ophthalmol, 127, 763-8.
10. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. (2003). Utility Assessment among patients with dry eye disease. Ophthalmology; 110: 1412-1419.

13 APPENDICES

Appendix 1 Schedule of Assessments (in recommended order)

Procedure	Visit 1 (Day1)[2]	Visit 2 (week 4 ± 2 days)	TC 1 (week 8 ± 2 days)	Visit 3 (week 12 ± 7 days)	TC 2 (week 16 ± 7 days)	TC 3 (week 22 ± 7 days)	Visit 4 (week 26 ± 7 days)	TC4 (week 30 ± 7 days)	TC5 (week 36 ± 7 days)	Visit 5 (week 40± 7 days	TC 6 (week 44 ± 7 days)	TC 7 (week 48 ± 7 days)	Visit 6/ET (week 52 ± 7 days)
Informed Consent / HIPAA	X[4]												
Medical / Surgical History and Demographics	X[3]												
Concomitant Medication	X[3]	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X[4]												
Urine Pregnancy Test (as needed)[1]	X[3]	X		X			X			X			X
Dryness Score (VAS severity of dryness)	X[3]	X		X			X			X			X
VAS	X[3]	X		X			X			X			X
OSDI	X[3]	X		X			X			X			X
Eyedrop Comfort and Acceptability Questionnaire													X
Visual Acuity (ETDRS)	X[3]	X		X			X			X			X
Slit-Lamp Biomicroscopy	X[3]	X		X			X			X			X
TFBUT	X[3]	X		X			X			X			X
Corneal Fluorescein Staining (NEI scale)	X[3]	X		X			X			X			X
Meibomian Gland Assessment (MGD score)	X[3]	X		X			X			X			X
Schirmer's Test I (without anesthesia)	X[3]						X						X
Intraocular Pressure	X[3]	X		X			X			X			X
Dilated Fundoscopy	X[3]			X			X			X			X
Adverse Event Query	X[4]	X	X	X	X	X	X	X	X	X	X	X	X
In-office instillation trial medication	X[4]												
Dosing Diary Dispensation/Review/Collection	X[4]	X		X			X			X			X
Dispensation of trial medication	X[4]			X			X			X			
Collection of trial medication				X			X			X			X
Trial Exit													X

[1] For women of childbearing potential
[2] For subjects continuing from NVU-003 to NVU-004, V1 of NVU-004 will be performed at V4 (Day 57) of NVU-003.
[3] Assessment Results being transferred from NVU-003 V4 (Day 57) to NVU-004 V1 (Day 1)
[4] Assessments to be performed for NVU-004

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 and 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.

Proper Handling of Eye drop Container

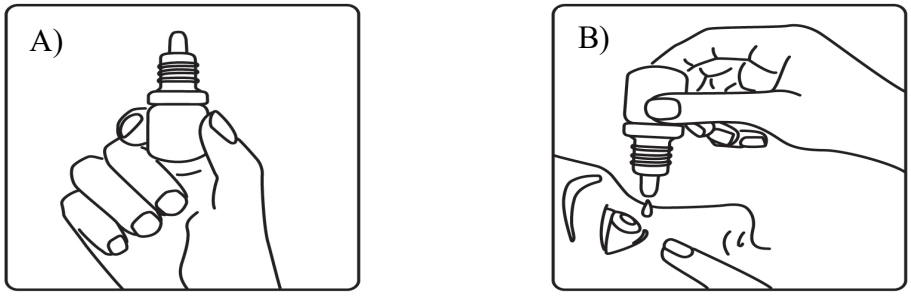


Figure A. Opening the bottle

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 the safety seal ring.
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.

Appendix 3 Examination Procedures, Tests, Equipment, and Techniques

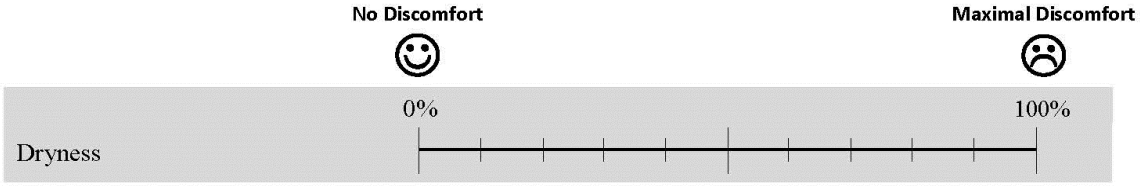
The following examination procedures, tests, equipment and techniques are listed in this Appendix:

- Dryness Score (VAS Severity of Dryness)
- Visual Analog Scale (VAS)
- Ocular Surface and Disease Index (ODSI©) questionnaire
- Visual Acuity
- Slit-Lamp Biomicroscopy
- Tear Film Break-up Time (TFBUT)
- Fluorescein Staining (NEI/Industry workshop Scale)
- Meibomian Gland Assessment (MGD score)
- Schirmer's Test I (without anesthesia)
- Procedure for Evaluating Intraocular Pressure
- Procedure for Conducting Dilated Fundoscopy
- Eyedrop Comfort and Acceptability Questionnaire
- Dosing Diary

Dryness Score

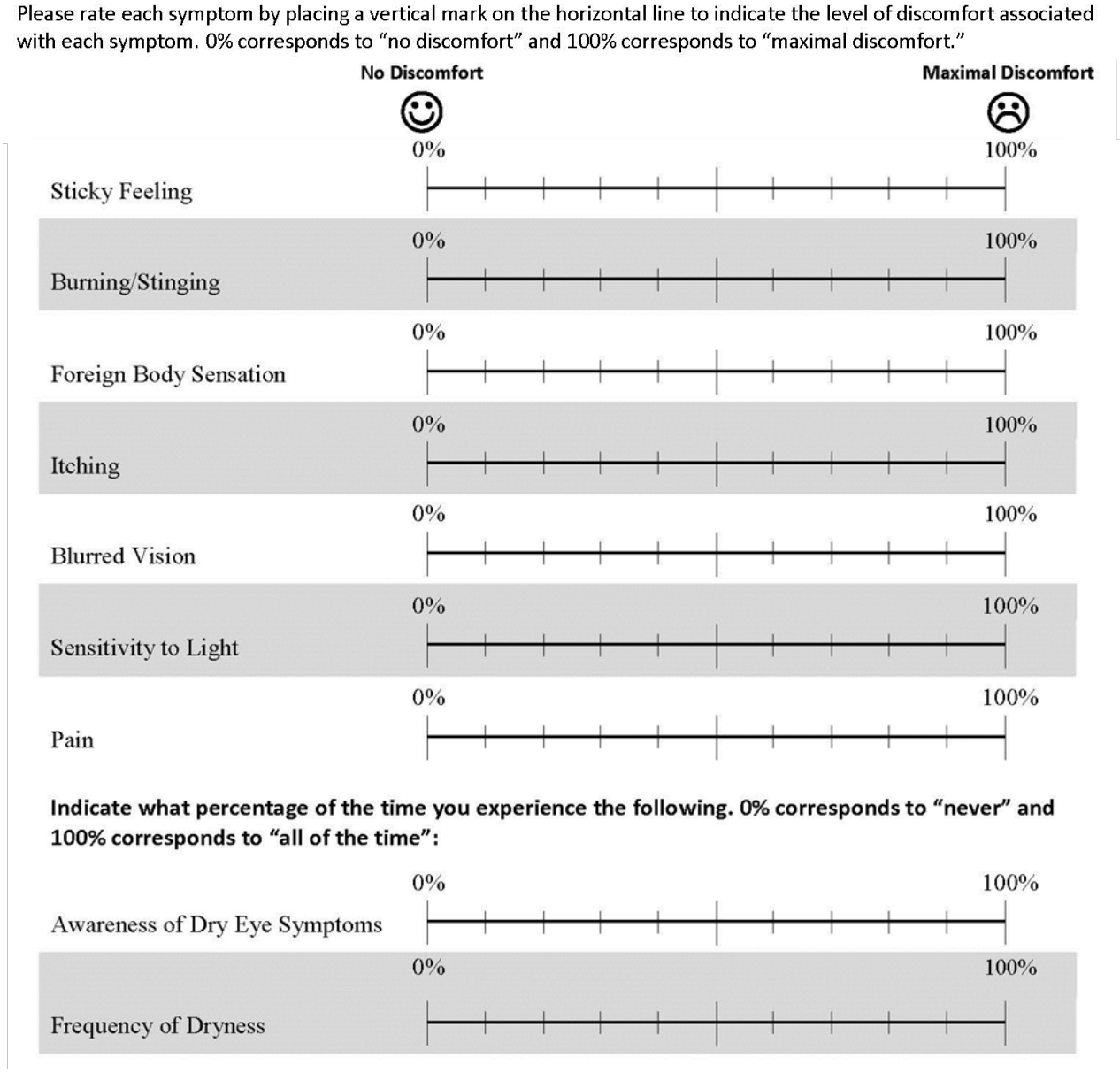
Study staff will ask subjects to rate their severity of ocular dryness (both eyes simultaneously) by placing a vertical mark on the horizontal line to indicate the level of discomfort (0 corresponds to "no dryness" and 100% corresponds to "maximal dryness"). The assessment line length of the scale will be 100 mm (10 cm) and will be according to the following depiction:

Please rate this symptom by placing a vertical mark on the horizontal line to indicate the level of discomfort associated with dryness. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort".



Visual Analog Scale (VAS)

Study staff will ask subjects to rate their ocular symptoms (both eyes simultaneously) due to ocular dryness by placing a vertical mark on the horizontal line to indicate the level of discomfort (0 corresponds to "no dryness" and 100% corresponds to "maximal dryness"). Subjects will be asked about the severity of dry eye symptoms: sticky feeling, burning / stinging, foreign body sensation, itching, blurred vision, sensitivity to light, and pain. Subjects will also be asked about their awareness of their dry eye symptoms and frequency of dryness. The assessment line length of the scale will be 100 mm (10 cm) and will be according to the following depiction:



Ocular Surface and Disease Index (OSDI)© questionnaire

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?.	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

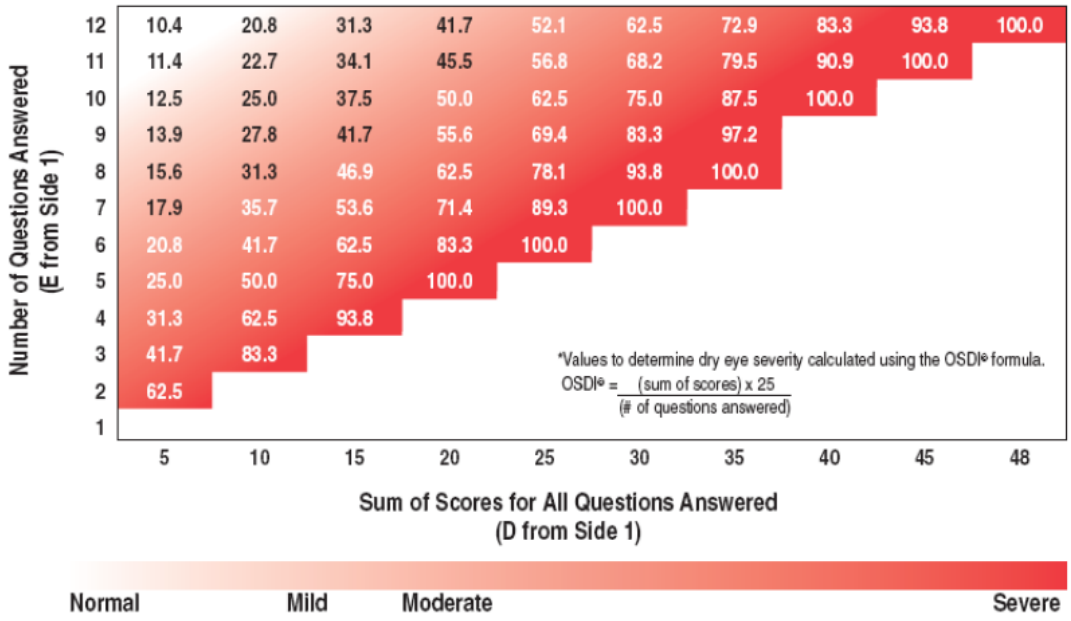
Please turn over the questionnaire to calculate the patient's final OSDI© score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Visual Acuity Procedures

LogMAR Visual Acuity (VA) must be assessed using an ETDRS-like chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye charts. Visual Acuity should be evaluated at the beginning of each visit in the study (i.e. prior to slit-lamp examination). Subjects should use the most recent correction to attain their best-corrected visual acuity (BCVA) during all VA assessments. Pinhole testing is not permitted.

Equipment

The visual acuity chart to be used is the ETDRS chart. In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only ETDRS Series 2000 Chart 1 & 2, and the right eye (OD) should be tested first. For reflectance (wall) charts,

the chart should be placed frontally and well illuminated. The subject viewing distance should be exactly 4 meters (13 feet).

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he/she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.
If the subject changes a response (e.g. 'that was a "C" not an "O"') before he/she has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.
A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, he/she should be encouraged to guess. If the subject identifies a letter as one of two letters, he/she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including in the last line read. This total sum represents the logMAR visual acuity for that eye.
For Example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 and on line 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	= 0.18

Repeat the procedure for the left eye (OS).
In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e. a subject forgets his/her glasses), the reason for the change in correction should be documented.
Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 0 (NVU-003) will be considered an Adverse Event.

Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described. The following will be examined at each visit:

- Lids
- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens

External magnification and biomicroscopy will be performed using a slit-lamp.

Magnification will be consistent with standard clinical practice. The subject will be seated for the assessment.

Tear Film Break-Up Time (TFBUT)

The examiner will instill 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. To thoroughly mix the fluorescein with the tear film, the subject will be instructed to blink several times. The examiner should wait approximately 30 seconds after instillation before evaluating TFBUT.

With the aid of a slit-lamp, the examiner will monitor the integrity of the tear film, noting the time it takes to form micelles from the time that the eye is opened. TFBUT will be measured in seconds using a stopwatch for the right eye followed by the left eye. The two TFBUT values that are used to calculate the average will be entered into the eCRF.

For each eye, two measurements will be taken and averaged unless the two measurements are >2 seconds apart and are each <10 seconds, in which case, a third measurement would be taken and the two closest of the three would be averaged. All values will be recorded in the source document.

Fluorescein Staining

The examiner will instill 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. Note, this is the same instillation as for TFBUT. To thoroughly mix the fluorescein with the tear film, the subject will be instructed to blink several times. The examiner should wait approximately 2-3 minutes after instillation before evaluating fluorescein staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will be graded with the NEI Grading Scale. Only the cornea will be graded. Digital images of fluorescein staining may be taken for digital analysis.

NEI/Industry Workshop Scale

For each eye, score each of the five areas of the cornea.

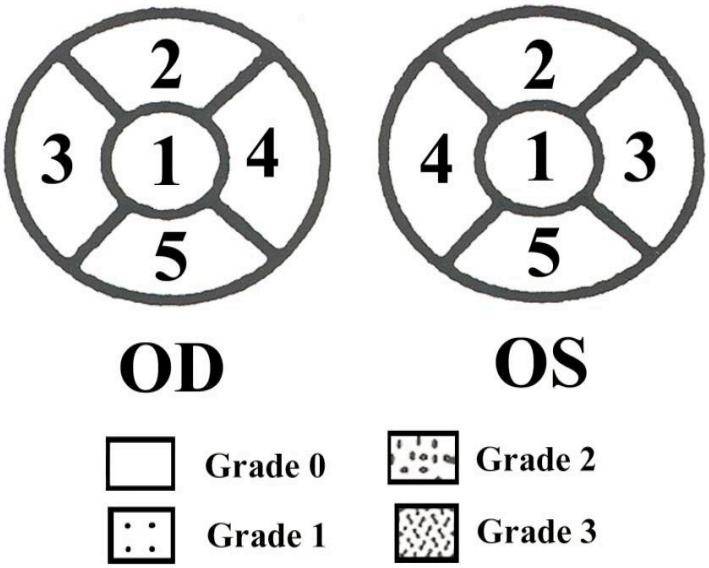


Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0-3 is used for each of the five areas on each cornea. Grade 0 will be specified when no staining is present. The maximum total score for each eye is 15.

Meibomian Gland Assessment (MGD score)

Meibomian gland dysfunction (MGD) is blockage or some other abnormality of the meibomian glands causing an insufficient secretion of lipids into the tear film. This causes the tears to evaporate too quickly, and thus MGD is considered a leading cause of dry eye syndrome.

The Meibomian Gland Evaluator stick (Korb MGE®-Stick) with standardized force application will be used for this assessment. The Meibomian Gland Assessment (MGD Score) will be performed during the trial at Visits 1 (transferred from V4 of NVU-003), 2, 3, 4, 5 and 6 or at an Early Termination Visit.

The secretion of 5 central glands on the lower eyelid will be evaluated for each eye. Each of the 5 glands will be scored from 0-3: **0 = normal, 1 = thick/yellow, whitish, particulate; 2 = paste; 3 = none/occluded**. The total score will thus range from 0-15.

In the NVU-003 study, i.e. as described in the subject's inclusion criteria, Meibomian Gland Dysfunction is defined as MGD score ≥ 3.

Schirmer's Test I (without anesthesia)

Schirmer Tear Test I will be performed during the trial at Visits 1 (transferred from V4 of NVU-003), 4, and 6, or at an Early Termination Visit. The test will be performed ≥5 minutes after MGD evaluation according to the following procedure:

- Do not blot eyes prior to the test.
- Using a sterile Schirmer test strip, a bend in the strip will be made in line with the notch in the strip.
- The subject will be instructed to gaze up and in.
- The Schirmer test strip will be placed in the lower temporal lid margin of each eye such that the strip fits tightly. Subjects will be instructed to close their eyes.
- After 5 minutes have elapsed, the Schirmer strip will be removed. The length of the moistened area will be recorded (mm) for each eye.

Procedure for Evaluating Intraocular Pressure

Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg at Visits 1 (transferred from V4 of NVU-003), 2, 3, 4, 5 and 6, or at an Early Termination Visit. A single measurement will be made to obtain a determination of IOP. The same tonometer employing the investigator's standard technique should be used throughout the trial. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

Procedure for Conducting Dilated Fundoscopy

A dilated fundoscopy exam will be performed during the trial at Visits 1 (transferred from V4 of NVU-003), 3, 4, 5 and 6 or at an Early Termination Visit. Observations will be graded as Normal or Abnormal. Abnormal findings will be described. The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve

Eyedrop Comfort and Acceptability Questionnaire

Eyedrop Comfort and Acceptability (4 Questions) will be scored on a visual analog scale ranging from 0 to 10. It will be assessed at Visit 6 (or an Early Termination visit) using the following Scale:

0	1	2	3	4	5	6	7	8	9	10
↑										↑
None/Not										Much/Very

Questionnaire Items

1. How satisfied are you with the study eye drop?
2. How comfortable did you find the study eye drop?
3. How easy was the administration of the study eye drop?
4. How high is the likelihood that you would ask for prescription of the study eye drops?

At-Home Dosing Diary

Subjects will be instructed how to complete the dosing diary and asked to complete a dosing diary entry for each dose taken daily.

Date DD/MMM/YYYY	Morning	Midday	Afternoon/ Early Evening	At Bedtime	Subject Initials
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	
___/____/_____	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	

Telephone calls: Non-leading AE questioning

The telephone calls are planned to check in with subjects about possible adverse events and any changes in medications throughout the study duration.

During the calls the following non-leading questions should be asked:

1. Does the subject take the study medication as prescribed.
2. Are there changes to the subjects` concomitant medication.
3. Does the subject experience any health problems.

Appendix 4 Amendment Summary of Changes

The Purpose of Protocol Amendment 2 dated 04 February 2020 (Protocol Version 3.0) is to implement updates and clarify several inconsistencies that are listed in the table below. Minor administrative corrections are not listed in the table below.

Section	Original Text	Amended Text (in bold)	Rationale
Header	13 December 2019 FINAL v2.0	**12 March 2020** FINAL **v3.0**	New version of protocol
Page 1	Version 2.0	Version **3.0**	New version of protocol
Page 1	(Added)	**Amendment 2: 12 MAR 2020**	Generation of amendment 2
Page 2	**Director Clinical Ophthalmology** Daniela Willen, PhD Tel: (0049) 6221-50259-142 dwillen@novaliq.com **Manager Clinical Operations** Anja Lange, Dipl.-Biol. Tel: (0049) 6221-50259-269 alange@novaliq.com	**Exc. Director –Clinical Affairs** **Jason Vittitow, PhD Tel: 908-541-3060 Jason.Vittitow@bausch.com** **Sr. Clinical Trial Manager** **Dan Donatello Tel: 585-338-5306 Daniel.donatello@Bausch.com**	Sponsor transfer
Page 2	**Clinical Project Manager:** Kristie Veasey Tel: (001) 919-595-0254 Fax: (001) 919-640-1663 Kristie.veasey@lexitas.com	**Nicole Derthick** Tel: 919-**699-9629** Fax: 919-640-1663 **Nicole.Derthick@lexitas.com**	Project manager change
Page 12, Abbreviations		**IMP Investigational Medicinal Product**	Added
Page 15	Summary of known and potential risks and benefits to human subjects		Section Deleted; as this information is present in the IB.
Page 4 and 19, Inclusion Criteria	Subjects must: 1. Have completed trial NVU-003 without major protocol deviations 2. Have a subject reported history of DED in both eyes	Subject Must: **1.** Have completed trial NVU-003 without major protocol deviations, **and have been compliant with NVU-003**	Added wording from inclusion criterion #3 to inclusion criterion #1.

	for at least 6 months prior to Visit 0 of NVU-003 and be diagnosed with DED at Visit 1 of NVU-003. 3. **Have been compliant with trial procedures and investigational product in NVU-003 according to the investigator`s assessment.** 4. Provide written informed consent. 5. Be able and willing to follow instructions, including participation in all trial assessments and visits.	**trial procedures and application of IMP.** 2. Have a subject reported history of DED in both eyes for at least 6 months prior to Visit 0 of NVU-003 and be diagnosed with DED at Visit 1 of NVU-003. 3. Provide written informed consent. 4. Be able and willing to follow instructions, including participation in all trial assessments and visits.	
Page 26, Section 8.1	In case clinical judgment considers it necessary, treatment with topical steroids (such as loteprednol etabonate, as recommended, not longer than 4 weeks at a time) or other topical prescription medications (such as cyclosporine, lifitegrast or serum tears) are allowed according to clinicians` prescription. Their use will be documented in the subject's source document and corresponding eCRF.	In case clinical judgment considers it necessary, treatment with topical steroids ~~**(such as loteprednol etabonate, as recommended, not longer than 4 weeks at a time)**~~ or other topical prescription medications ~~**(such as cyclosporine, lifitegrast or serum tears)**~~ are allowed according to clinicians` prescription. Their use will be documented in the subject's source document and corresponding eCRF.	Removed specific drug names as deemed not necessary to provide this level of detail.
Page 30, Section 8.6.2	• Adverse events; • Protocol violations; • Lack of efficacy; • Administrative reasons (e.g. inability to continue, lost to follow up); • Sponsor termination of trial; • Subject choice (e.g. withdrawal of consent); • Other	**•Adverse event;** **•Lack of efficacy;** **•Withdrawal by subject;** **•Protocol violation;** **•Lost to follow up;** **•Sponsor termination of trial;** **•Death** **•Other**	Updated list to match CRF reasons for d/c.
Page 38, Section 10.1	Data will be summarized by treatment group as assigned in NVU-003 and overall. Group 1 and group 2 consist of subsets of subjects who received masked treatment with NOV03 or saline, respectively, in NVU-003.	Data will be summarized by treatment group as **received** in NVU-003 and overall. Group 1 and group 2 consist of subsets of subjects who received masked treatment with NOV03 or saline, respectively, in NVU-003.	Updated by stats
Page 38, Section 10.3	Therefore, with 100 subjects completing week 52 (or week 26) of treatment, if an adverse event of a specific type is not observed,	~~**Therefore, with 100 subjects completing week 52 (or week 26) of treatment, if an adverse event of a specific type is not**~~	Deleted by stats

	then with 95% confidence, the true incidence rate of the adverse event is less than 3.0%.	~~**observed, then with 95% confidence, the true incidence rate of the adverse event is less than 3.0%.**~~	
Page 39, Section 10.4.1		The results of assessments performed at multiple visits will be presented by visit as appropriate unless otherwise specified. The results of bilateral ocular assessments will be summarized separately for study and fellow eyes.	Added by stats
Page 39, Section 10.4.5	Dosing information will be summarized overall and by treatment from NVU-003 and listed for each subject. Discontinuation of treatment will be summarized. The primary reason for IMP discontinuation will also be summarized by treatment group as assigned in NVU-003. Adverse events (AEs) will be coded using the MedDRA dictionary. An AE is treatment emergent if it occurs or worsens after the first dose of trial treatment in clinical trial NVU-004. Frequencies and percentages of subjects with TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided. 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.	Dosing information will be summarized overall and by treatment from NVU-003 and listed for each subject. Discontinuation of treatment will be summarized. The primary reason for IMP discontinuation will also be summarized by treatment group as **received** in NVU-003. Adverse events (AEs) will be coded using the MedDRA dictionary. An AE **will be defined as** treatment emergent if it occurs or worsens after the first dose of trial treatment in clinical trial NVU-004. Frequencies and percentages of subjects with TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided. 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 **provided** for ocular and non-ocular AEs. **Ocular AEs will be summarized at the subject level, at the eye level and separately for study and fellow eyes.**	Updated by stats

Page 40	Other safety endpoints including those assessed by visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by visit and by treatment group as assigned in NVU-003 using descriptive statistics. Changes from baseline (as defined in clinical trial NVU-003) will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.	Other safety endpoints including ~~**those assessed by**~~ visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by visit and by treatment group as **received** in NVU-003 using descriptive statistics. Changes from baseline (**baseline** as defined in clinical trial NVU-003) will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.	Updated by stats
Section 4.3	The results of assessments at Visit 4 (Day 57) in study NVU-003 (=final visit) will be taken as Day 1 data for NVU-004. Further data/assessments to be captured will be the NVU-004 Informed Consent, Inclusion/Exclusion Criteria to determine NVU-004 eligibility, and IMP dispensation.	The results of assessments at Visit 4 (Day 57) in study NVU-003 (=final visit) will be taken as Day 1 data for NVU-004. Further data/assessments to be captured will be the NVU-004 Informed Consent, Inclusion/Exclusion Criteria to determine NVU-004 eligibility, **Non-leading Adverse Event questioning (AE query)** and IMP dispensation.	Clarification of requirements at Visit 1.
Appendix 1, Visit 1 (Day 1)	Adverse Event Query X[3]	Adverse Event Query X[4]	Clarification of requirements at Visit 1.
Appendix 3, MGD Score on page 55	In this study, i.e. as described in the subject's inclusion criteria, Meibomian Gland Dysfunction is defined as MGD score ≥ 3.	In **the NVU-003** study, i.e. as described in the subject's inclusion criteria, Meibomian Gland Dysfunction is defined as MGD score ≥ 3.	Clarification that MGD score is evaluated for inclusion at NVU-003 only.
Appendix 3, Procedure for Evaluating IOP on page 56	Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg at Visits 0 and 4, and at an Early Termination Visit.	Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg at **Visits 1 (transferred from V4 of NVU-003), 2, 3, 4, 5 and 6**, and at an Early Termination Visit.	Clarification of visit schedule for IOP assessment.
Appendix 3, Procedure for Conducting Dilated Fundoscopy	A dilated fundoscopy exam will be performed during the trial at Visits 0 (Screening) and 4 and at an Early Termination Visit.	A dilated fundoscopy exam will be performed during the trial at **Visits 1 (transferred from V4 of NVU-003), 3, 4, 5 and 6** and at an Early Termination Visit.	Clarification of visit schedule for Dilated Fundoscopy assessment.

Appendix 3, Eyedrop Comfort and Acceptability Questionnaire	Eyedrop Acceptability Questionnaire Eyedrop Acceptability (3 Questions) will be scored on a visual analog scale ranging from 0 to 10. It will be assessed at Visit 4 using the following Scale: Questionnaire Items 1. How satisfied are you with the study eye drop? 2. How easy was the administration of the study eye drop? 3. How high is the likelihood that you would ask for prescription of the study eye drops?	Eyedrop **Comfort and** Acceptability Questionnaire Eyedrop **Comfort and** Acceptability (**4** Questions) will be scored on a visual analog scale ranging from 0 to 10. It will be assessed at Visit **6 (or at an Early Termination Visit)** using the following Scale: Questionnaire Items 1. How satisfied are you with the study eye drop? **2. How comfortable did you find the study eye drop?** 3. How easy was the administration of the study eye drop? 4. How high is the likelihood that you would ask for prescription of the study eye drops?	Clarification of visit schedule. Name change and question added.
Appendix 5	(Added)	**Amendment 2: 12 MAR 2020**	Generation of Amendment 2
Appendix 5	Sponsor signatories from Novaliq (Daniela Willen, Anja Lange, Sonja Krösser, PhD, Gabriela Burian) and Lexitas (Kristie Veasey)	Sponsor signatories from B+L (Johnson Varughese, Jason Vittitow, Gary Mosehauer, Robert Kang, Mary Harrell, Binu Alexander) and Lexitas (Joanna Williams)	Change of contacts for study
Appendix 6	(Added)	**Amendment 2: 12 MAR 2020**	Generation of Amendment 2

Appendix 5 Sponsor and CRO Approvals

Protocol Title:	A Phase 3, Multi-Center, Open-Label Extension (OLE) Clinical Trial to Assess the Extended Long-Term Safety and Tolerability of NOV03 (Perfluorohexyloctane) in Subjects who Completed Trial NVU-003 (Kalahari OLE)
Protocol Number:	NVU-004
Original Protocol:	14 OCT 2019
Amendment 1	13 DEC 2019
Amendment 2	12 MAR 2020

This clinical trial protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing, reviewing and/or approving this protocol.

Signed: _____ Date: 22/Jun/2020
Johnson Varughese
VP, Clinical Services, Bausch Health US, LLC

Signed: _____ Date: 10 Jun 2020
Jason Vittitow, PhD
Exc. Director - Clinical Affairs, Bausch Health US, LLC.

Signed: _____ Date: 20 May 2020
Gary Moschauser, MS
Director, Biostatistics, Bausch & Lomb Incorporated

Signed: _____ Date: 10 JUN 2020
Robert Kang
Senior Director, Data management, Bausch Health US, LLC.

Signed: p.p. _____ (AMRITA RAMAN) Date: 26 JUN 2020
Mary Harell
Senior Director, Global Regulatory Affairs, Bausch Health US, LLC.

Signed: _____ Digitally signed by Binu Alexander DN: dc=com, dc=BHCorp, dc=Valeant, ou=North America, ou=Bridgewater, ou=Users, ou=Employees, cn=Binu Alexander Date: 2020.06.10 15:01:58 -04'00' Date: 10 JUN 2019
Binu J. Alexander MD
Executive Director, Global Pharmacovigilance and Risk Mananment, Bausch Health US, LLC.

Signed: _____ Date: 29Jun 2020
Joanna Williams
Chief Operating Officer, Lexitas Pharma

Signed: _____ Date: 29 JUN 2020
Kenneth Sall
Medical Monitor

Appendix 6 Investigator's Signature

Protocol Title:	A Phase 3, Multi-Center, Open-Label Extension (OLE) Clinical Trial to Assess the Extended Long-Term Safety and Tolerability of NOV03 (Perfluorohexyloctane) in Subjects who Completed Trial NVU-003 (Kalahari OLE)
Protocol Number:	NVU-004
Date:	14 OCT 2019
Amendment 1	13 DEC 2019
Amendment 2	12 MAR 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: _____