Nicox Ophthalmics, Inc.

4721 Emperor Blvd., Durham, North Carolina 27703 USA

Compound:
NCX 4251

Study Number:
NCX-4251-02

Study Title:
A Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Phase 2b Study Evaluating the Safety and Efficacy of NCX 4251 (Fluticasone Propionate Nanocrystal) Ophthalmic Suspension, 0.1% QD for the Treatment of Acute Exacerbations of Blepharitis (Mississippi)

PROTOCOL

Version # 4.0

Released on 24-March-2021

Clinical Development Phase: 2b

Sponsor: **Nicox Ophthalmics, Inc.**
4721 Emperor Blvd.
Durham, North Carolina 27703 – USA

NCT04675242

PROTOCOL SIGNATURE PAGE

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APPROVAL OF STUDY PROTOCOL

Version: Version 4.0
Release Date: 24-March-2021

Site Details (Address and Telephone Number):

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The undersigned confirms that:

- This protocol has been read in its entirety and agreed to all aspects.
- This study will be implemented and conducted diligently and in strict compliance with the protocol, Good Clinical Practices, and all applicable laws and regulations.
- All information supplied by Nicox or its legal representatives will be maintained in confidence and, when this information is submitted to an Institutional Review Board (IRB) it will be submitted with a designation that the material is confidential.

Principal Investigator:

(Printed Name)	Date	Signature

Sponsor: Nicox Ophthalmics, Inc.
4721 Emperor Blvd., Durham, NC 27703 USA

On behalf of the Sponsor:

DocuSigned by:
José L. Boyer
Signer Name: José L. Boyer
Signing Reason: I approve this document
Signing Time: 24 March 2021 | 1:00:00 PM PDT
52488AFF4443453E9DB3CD8276742EF8

24 March 2021

José L. Boyer, PhD
Vice President, Head of Research and Development

Signature and Date

CONTACT INFORMATION

Protocol Identification
A Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Phase 2b Study Evaluating the Safety and Efficacy of NCX 4251 (Fluticasone Propionate Nanocrystal) Ophthalmic Suspension, 0.1% QD for the Treatment of Acute Exacerbations of Blepharitis (Mississippi)

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PROTOCOL HISTORY TABLE

VERSION #	VERSION DATE	REASONS FOR CHANGE(S)	DETAILS OF CHANGE(S)
1.0	04-Nov-2020	Original version	Not applicable
2.0	06-Nov-2020	• Alignment with primary analyses of the secondary efficacy endpoints	• [redacted]
3.0	22-Jan-2021	• Administrative	• Updated contact information [redacted]
		• Alignment with timing of eyelid scrubs and study medication application on non-visit days, and scheduling logistics related to [redacted]	• Revised window for timing of eyelid evaluations [redacted]
		• Occurs after the last on-treatment efficacy evaluations	• Removed Day 15 application of study medication (Synopsis; section 3.1; section 6.10; section 7.5; Appendix 1)
		• Clarifications	• Study medication should only be dispensed by the site designee (section 6.8) • Clarified text regarding calculation of logMAR VA (Appendix 2, section 4)
4.0	24-Mar-2021	• Enhance enrollment	• Revised Exclusion Criteria #2 to permit inclusion of subjects who had prior eyelid surgery provided it was >4 years prior to the Screening Visit and clarify exclusion if eyelid surgery was within 4 years of the Screening Visit (Synopsis, section 4.4)

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LIST OF ABBREVIATIONS	
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BID	*Bis in die* (twice daily)
CFR	Code of Federal Regulations
CI	Confidence Interval
COV	Close Out Visit
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CSR	Clinical Study Report
DMP	Data Management Plan
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
FP	Fluticasone Propionate
GCP	Good Clinical Practice
GRVD	Graft-Versus-Host-Disease
HDPE	High Density Polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic Pituitary Adrenal
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
[redacted]	[redacted]
logMAR	Logarithm of Minimum Angle Resolution
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
MMP	Monitoring Management Plan
mmHg	Millimeters of Mercury
[redacted]	[redacted]
ND	Not Done
NDA	New Drug Application
OAG	Open-Angle Glaucoma

OD	*Oculus Dexter* (right eye)
ODS	Ocular Discomfort Scales
OHT	Ocular Hypertension
OS	*Oculus Sinister* (left eye)
OU	*Oculus Uterque* (both eyes)
PI	Principal Investigator
PP	Per Protocol
QD	*Quaque Die* (once daily)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SDV	Source Data Verification
SMP	Safety Management Plan
TEAE	Treatment Emergent Adverse Event
TFBUT	Tear Film Break Up Time
U.S.	United States
VA	Visual Acuity
VAS	Visual Analogue Scale
WHO	World Health Organization

Note: the first occurrence of some abbreviations is not spelled out in the document (e.g., units of measure).

STUDY OUTLINE / PROTOCOL SYNOPSIS

Title	A Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Phase 2b Study Evaluating the Safety and Efficacy of NCX 4251 (Fluticasone Propionate Nanocrystal) Ophthalmic Suspension, 0.1% QD for the Treatment of Acute Exacerbations of Blepharitis (Mississippi)
Study No.	NCX-4251-02
Sponsor	Nicox Ophthalmics, Inc.
Background and Rationale	NCX 4251 (fluticasone propionate nanocrystal) Ophthalmic Suspension is a sterile, preserved, topical ocular suspension of fluticasone propionate nanocrystals packaged in multi-dose ophthalmic dropper bottles, and is being developed for the treatment of acute exacerbations of blepharitis by topical application directly to the site of the inflammation at the eyelid margin. Nicox Ophthalmics, Inc. (Nicox) developed a novel formulation and route of delivery consisting of applying NCX 4251 directly to the eyelids designed to minimize the intraocular exposure to fluticasone. The safety and tolerability of NCX 4251 ophthalmic suspension, 0.1% in subjects with an acute exacerbation of blepharitis and signs and symptoms of dry eye disease was evaluated in a multi-center, randomized, double-masked, placebo-controlled, two-cohort, phase 2 study (NCX-4251-01). In Cohort 1 of the study, 15 subjects with ongoing active signs and symptoms of blepharitis evidenced by elevated eyelid discomfort, eyelid redness and eyelid debris accompanied by concurrent signs and symptoms of dry eye were randomized to NCX 4251 ophthalmic suspension 0.1% or placebo (2:1 ratio, 10 subjects on NCX 4251 and 5 subjects on placebo). Subjects additionally performed daily eyelid scrubs with baby shampoo and were treated once daily (QD) for 14 days, followed by a 14-day eyelid scrubs only safety follow-up period. In Cohort 2, 21 subjects were randomized to NCX 4251 Ophthalmic Suspension 0.1% twice daily (BID) or placebo BID (1:1 ratio) and performed daily lid scrubs with baby shampoo and were treated for 14 days, followed by a 14-day eyelid scrubs only safety follow-up period. The interim analysis performed on Cohort 1 indicated that NCX 4251 and the new route of administration were well tolerated, and that no clinically relevant intraocular pressure (IOP) elevations were observed in the study. Although the study was not powered for efficacy, changes in magnitude of clinical relevance were observed in signs and symptoms of blepharitis and dry eye. [redacted] Blepharitis, a chronic inflammatory condition of the eyelid margin, is one of the most common ocular disorders seen by ophthalmic practitioners and is recognized to have a significant impact on ocular comfort and quality of life (Buchholz, 2006; Duncan, 2015). It often has a chronic manifestation with intermittent exacerbations defined by an increase in symptoms. Signs and symptoms of blepharitis include burning, itchiness, gritty feeling in the eyes, contact lens intolerance, photophobia, redness (telangiectasia), swelling, discomfort and crusting of the eyelid margins (Lindsley et al, 2012). While generally not sight-threatening, blepharitis can induce

	permanent eyelid margin alterations (eyelid notching and scarring, loss of eyelashes, in-turning of eyelashes) and even vision loss from superficial keratopathy, corneal neovascularization, or ulceration. Chronic blepharitis can also lead to destruction of the meibomian gland architecture and closure of the orifices by scar tissue (AAO PPP, 2013; Foulks, 2009). Blepharitis affects all ages and ethnic groups. While children can develop blepharitis, onset is typically during middle age. Although blepharitis is commonly encountered in clinical practice, its true incidence and prevalence in the general population has not been well documented apart from some regional studies. In one survey, ophthalmologists and optometrists in the United States reported that 37% to 47% of their patients had evidence of blepharitis (AAO PPP, 2013; Lemp, 2009). Even though the treatment of chronic blepharitis remains controversial, palpebral neutral shampoo cleaning has been the most widely accepted medical therapy in the U.S., followed by the use of antibiotic, or combination of antibiotic and steroid ointments. Short courses of topical steroids have been found beneficial for symptomatic relief in cases with clinically significant ocular inflammation in acute exacerbations of all forms of blepharitis (Lindsley et al, 2012; AAO PPP, 2013, Arrua, 2015; Pflugfelder, 2014; Jackson, 2008). Topical ocular corticosteroids, including 0.5% loteprednol etabonate and 0.1% dexamethasone, in combination with topical ocular antibiotics, have been effective in reducing the signs of blepharitis, with some differences in safety profile with respect to IOP (Pflugfelder et al, 2014; Hosseini et al, 2016; Comstock et al, 2017). No clinical trials have evaluated topical ocular steroids applied directly to the eyelid margin; the site of blepharitis. Eyelid margin application may avoid ocular side effects of topical ocular corticosteroids, including IOP elevation. Although fluticasone propionate (FP) demonstrates greater activity than other corticosteroids of similar potency in vasoconstrictor assays in humans, FP used in the treatment of inhalation, intranasal or dermatological disorders demonstrates low potential to cause significant suppression of the hypothalamic-pituitary-adrenal (HPA) axis (Spencer and Wiseman, 1997; Johnson, 1998; Korting and Schöllmann, 2012). FP is a synthetic tri-fluorinated corticosteroid of medium potency (class III) with high affinity for the glucocorticoid receptor, high lipophilicity, rapid hepatic biotransformation and a favorable benefit/risk ratio (Johnson, 1998; Korting and Schöllmann, 2012). Like other topical dermal corticosteroids, FP has anti-inflammatory, immunosuppressive, antipruritic, and antiproliferative effects, which is thought to be its primary mechanism of action in the treatment of several skin disorders (Roeder et al, 2005; Cutivate Lotion US Prescribing Information, 2015). FP is a locally active glucocorticoid which has no demonstrable systemic side-effects when given by the oral or topical routes, as it appears to be extracted totally during its 'first pass' from the gut through the liver. FP has an established nonclinical and clinical safety profile as inhalation, nasal, and dermal formulations. FP is marketed for the treatment of asthma (Flovent® HFA, NDA 021433, Advair® DISKUS®, NDA 021077), rhinitis (Flonase® NDA 020121), and atopic dermatitis (Cutivate®, NDA 021152). Nicox is developing NCX 4251 for the treatment of acute exacerbations of blepharitis to address the current unmet medical need.
Study Period	Q4 2020 to Q4 2021
Study Phase	Phase 2b

Study Design	This is a multi-center, randomized, double-masked, placebo-controlled, Phase 2b study evaluating the safety and efficacy of NCX 4251 (fluticasone propionate nanocrystal) Ophthalmic Suspension 0.1% QD for the treatment of acute exacerbations of blepharitis.
Number of Subjects	This study will be conducted in approximately 5 to 10 sites in the United States. Approximately 300 subjects will be screened and approximately 200 will be randomized.
Study Objectives	The objective of this clinical study is to evaluate the safety and efficacy of NCX 4251 Ophthalmic Suspension, 0.1% vs. placebo for the treatment of the signs and symptoms of blepharitis
Selection of Target Subject Population	The target population in this study will be adult men and women with a documented history of blepharitis who are currently experiencing signs and symptoms of blepharitis. The blepharitis signs and symptoms required for inclusion in the study are defined as a minimum score of '1' (on a 4-point scale) for each of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort [redacted] at the Screening and Baseline/Day 1 Visits.
Study Medication, Comparator, Dosage and Mode of Application	Subjects will be randomized in a 1:1 ratio to receive either NCX 4251 Ophthalmic Suspension 0.1% QD or Placebo (vehicle of NCX 4251 ophthalmic suspension) QD. Study medication will be applied via a sterile applicator to the upper and lower eyelid and lower eyelid margin of both eyes once daily in the morning for 14 days. In addition, all subjects will perform daily morning eyelid scrubs of the upper and lower eyelids of both eyes using diluted baby shampoo applied with a cotton swab prior to the application of the study medication during the treatment period. On the days of study visits, morning eyelid scrubs and application of study medication will be performed by the subject at the clinical site. Morning eyelid scrubs will continue from study medication discontinuation until the Day 29/Exit Visit.
Study Conduct and Duration of Treatment	Subjects will be evaluated at 7 clinical visits over a period of approximately 6 weeks. Eligible adult subjects with signs and symptoms of blepharitis defined as a minimum score of '1' (on a 4-point scale) for each of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort [redacted] at both the Screening and Baseline/Day 1 Visits will be randomized on Day 1. Study visits will be as follows: Screening (Day -14 to -7), Baseline/Day 1, Day 4 (± 1 day), Day 8 (± 1 day), Day 11 (± 1 day), Day 15 (- 1 day), and Day 29/Exit (± 2 days; follow up visit).

Inclusion Criteria	Subjects must fulfill the following criteria: 1) be at least 18 years of age; 2) have a documented history of blepharitis of at least 6 months; 3) be currently experiencing an acute exacerbation of blepharitis defined as a minimum score of '1' for each of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort [redacted] at both the Screening and Baseline/Day 1 Visits; 4) have a Best Corrected Visual Acuity (BCVA) of +0.60 logMAR (approximately 20/80 Snellen) or better in each eye as measured using an ETDRS chart with the subject wearing their habitual correction or with pinhole refraction; 5) be able to perform eyelid scrubs with diluted baby shampoo and apply study medication satisfactorily, in the opinion of the Investigator; 6) if female, must either be incapable of pregnancy because of hysterectomy, bilateral tubal ligation, or bilateral oophorectomy, or be post-menopausal (have been amenorrheic for at least 2 years) or must use an effective method of birth control for the duration of the study. Female subjects of childbearing potential must have a negative urine pregnancy test and not be breastfeeding or planning a pregnancy; 7) be able to provide written informed consent and sign the HIPAA form to participate in the study, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local regulations, before initiating any study-related procedures; and 8) be able and willing to comply with treatment and all study procedures.
Exclusion Criteria	1) have an Eyelid Debris score of 3 or have cylindrical collarettes in either eye; 2) have clinically significant abnormality of the eyelids or lashes (e.g., entropion, ectropion) other than blepharitis, or have a history of lagophthalmos or trichiasis; or have had eyelid surgery (including blepharoplasty) within 4 years of the Screening Visit. Eyelid surgery performed >4 years prior to the Screening Visit is permitted provided there is normal apposition of the eyelids upon closure and that there is no residual lagophthalmos, no distortion of the lid margin and no abnormal lid function resulting in potentially increased exposure of the ocular surface; 3) have received an injection of Botulinum toxin (Botox or equivalent) in the periocular area within 3 months prior to the Screening Visit; 4) have any current or recurrent ocular infections (bacterial, viral or fungal), active ocular inflammation other than blepharitis or dry eye (i.e., follicular conjunctivitis, iritis) or preauricular lymphadenopathy; 5) have current or recurrent diagnosis of ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis (e.g., confluent epithelial loss or any infiltrates); 6) have been diagnosed with glaucoma or ocular hypertension, or have an IOP > 21 mmHg at the Screening Visit or Baseline/Day 1 Visit;

	7) have a history of IOP elevation with steroid use (i.e., steroid responder); 8) unable or unwilling to discontinue the use of contact lenses from Screening to Day 29/Exit Visit; 9) use any eye makeup (including on the eyelids, eyelid margins, and lashes) at the Screening Visit and unwilling to cease the use of eye make-up up to the Day 15 Visit; 10) cosmetic eyelash procedures (e.g., eyelash curling) from the Screening Visit up to the Day 15 Visit, or a history of permanent/semi-permanent eye make-up procedure (e.g., eyelash extensions / false eyelashes, eyelash tinting, eyeliner tattooing) within 30 days of the Screening Visit or planned procedure during the study period; 11) have permanent punctal plugs or history of nasolacrimal obstruction; 12) have a history of ocular surgical intervention within 6 months prior to the Screening Visit or any planned ocular procedure during the study period; 13) have known hypersensitivity to fluticasone propionate, to any other component of the study medication, or to ophthalmic diagnostic dyes [redacted] 14) use strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin); 15) unable or unwilling to discontinue use of any non-diagnostic ophthalmic treatments (topical, intraocular or systemic) including topical autologous serum eyedrops, artificial tears and ocular lubricants. Subjects should not have used artificial tears or ocular lubricants for at least 24 hours prior to the Screening Visit, and for at least 30 days for all other ophthalmic medications; 16) unable or unwilling to discontinue use of any non-diagnostic ophthalmic procedures [redacted] from the Screening Visit through the study period. Warm compresses and the subject's routine eyelid scrubs are permitted from the Screening Visit through the evening prior to Baseline/Day 1 Visit, and protocol-specified eyelid scrubs from Baseline/Day 1 through the study period; 17) have a history of meibomian gland probing within 3 months prior to the Screening Visit; 18) use of any corticosteroid agent or anabolic steroid within 30 days of the Screening Visit or during the study treatment period; 19) use of isotretinoin or any other retinoids within 12 months of the Screening Visit; 20) have any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, diabetes, cystic fibrosis) in the opinion of the Investigator; 21) have thyroid ophthalmopathy, rosacea or seborrheic dermatitis; 22) have any auto-immune disease (e.g., rheumatoid arthritis, lupus, Sjogren's, graft-versus-host disease (GVHD)). Note: Patients with controlled, mild rheumatoid arthritis without any other component (e.g., psoriatic) are allowed

	to be included in the study; 23) have a condition which, in the Investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation or their ability to perform eyelid scrubs and apply the study medication; 24) have participated in any drug or device study within 30 days prior to the Screening Visit and/or planning to participate in any other study while participating in the current study; and 25) were randomized in the NCX-4251-01 clinical trial.
Study Endpoints	**Primary Efficacy Endpoint** • Proportion of subjects with Complete Cure (Score 0) in each of the following: Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at the Day 15 Visit **Secondary Efficacy Endpoint** • Mean change from baseline in the Eye Dryness Symptoms using the Visual Analogue Scale (VAS) at the Day 15 Visit; • Mean change from baseline in Fluorescein Staining of the inferior cornea at the Day 15 Visit. [redacted]

	• [redacted] • [redacted].
	Safety • The incidence of treatment emergent ocular and systemic adverse events (AEs); • BCVA, IOP, ocular signs (as assessed by slit lamp biomicroscopy), and fundus assessments.
Statistical Methods	**Sample size determination and efficacy analyses:** The primary objective of this study is to demonstrate that the proportion of subjects with complete cure (score =0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at Day 15 for NCX 4251 treated subjects is statistically superior to placebo treated subjects using a 2-sided alpha = 0.05. For the complete cure endpoint, [redacted] approximately 208 subjects randomized overall (~104 subjects randomized per treatment group, [redacted] yield: • [redacted] to demonstrate statistical superiority to placebo The above analysis assumed a Day 15 time point; [redacted] and a two-sided significance level of 5% using a Fisher's exact test. The secondary objective of this study is to demonstrate that mean reduction from baseline in Eye Dryness evaluated on VAS and/or Fluorescein Staining of inferior cornea at Day 15 for NCX 4251 are statistically superior to placebo using a Hochberg procedure to maintain the overall Type I Error rate = 0.05. For the Eye Dryness endpoint, [redacted] approximately 124 subjects randomized overall (~62 subjects randomized per treatment group, [redacted]: • [redacted] to demonstrate statistical superiority to placebo The above analysis assumed a Day 15 time point; [redacted] a common standard deviation (SD) of 20 points and a two-sided significance level of 0.025 using a two-sample t-test. For Fluorescein Staining of inferior cornea, a [redacted] approximately 72 subjects randomized overall (~36 subjects randomized per treatment group, [redacted] • [redacted] to demonstrate statistical superiority to placebo The above analysis assumed a Day 15 time point; [redacted] and

a two-sided significance level of 0.025 using a two-sample t-test.

The study will be considered a success and NCX 4251 will be claimed to be superior to placebo in the proportion of subjects with complete cure (score =0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at Day 15 if the primary endpoint is demonstrated to be statistically significant in favor of NCX 4251.

Statistical inference will be made on the two secondary endpoints only if the primary endpoint demonstrates statistical significance in favour of NCX 4251. Multiplicity correction within the two secondary efficacy endpoints will be completed using Hochberg's procedure.

[redacted]

Summaries for continuous variables will include the sample size, mean, standard deviation, standard error, median, minimum, and maximum. Summaries for discrete variables will include frequency counts and percentages. The Baseline measure will be defined as the last non-missing measure prior to initiation of study treatment. Baseline value will be the last non-missing measure prior to initiation of study treatment. Analyses will be completed on the study eye and fellow eye separately. Additional analyses may be completed using both eyes within a model accounting for the correlation between eyes within a subject and will be detailed in the formal statistical analysis plan.

[redacted]

Efficacy analyses

Complete cure (score =0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort will be summarized using discrete summary statistics (frequency counts and percentages) as well as two-sided 95% Clopper-Pearson confidence intervals by treatment group. The primary efficacy analyses will test the difference in the proportion of study eyes with complete cure in the composite score between NCX 4251 Ophthalmic Suspension and placebo at Day 15 using a generalized estimating equation model with complete cure as the response, treatment as a fixed effect and baseline composite score as a covariate. The, marginal proportions and difference in proportions along with the corresponding two-sided 95% Confidence Intervals (CIs) and p-value will be presented.

Secondarily, differences (NCX 4251 Ophthalmic Suspension minus placebo) between treatment groups will be summarized using difference in proportions, 95% asymptotic confidence intervals around the differences in proportions, and Pearson's chi-squared test. [redacted]

[redacted]

[redacted]

Secondary endpoints will be summarized using continuous summary statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) as well as two-sided 95% t-distribution confidence intervals around the mean by treatment group. The primary analysis of the secondary endpoints will employ a linear model with mean change from baseline in Eye Dryness evaluated on the VAS and mean change from baseline in Fluorescein Staining of the inferior cornea at Day 15 as the response and baseline eye dryness as a covariate. Least squared means and differences between treatment groups, along with corresponding 95% CIs and p-values will be presented.

[redacted]

Safety analyses

Adverse events (AEs) will be coded using the MedDRA dictionary. The safety analysis will summarize treatment emergent ocular and systemic AEs for all treated subjects, using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group.

A treatment-emergent AE (TEAE) is defined as an AE that occurred on or after the treatment was initiated. Ocular TEAEs by treatment group: NCX 4251 0.1% and placebo will be summarized, by relationship to study drug, and by severity. Non-ocular TEAEs will be summarized by treatment group as follows: non-ocular TEAEs, by relationship to study, and by severity. Serious AEs (SAEs), AEs resulting in study drug discontinuation, and deaths will be presented in data listings.

Other ocular safety data including visual acuity, slit-lamp biomicroscopy, IOP, and dilated ophthalmoscopy will be summarized by treatment group and visit using

	descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

1. INTRODUCTION

1.1 Background and Rationale

NCX 4251 (fluticasone propionate nanocrystal) Ophthalmic Suspension is a sterile, preserved, topical ocular suspension of fluticasone propionate nanocrystals packaged in multi-dose ophthalmic dropper bottles, and is being developed for the treatment of acute exacerbations of blepharitis and dry eye disease by topical application directly to the site of the inflammation at the eyelid margin. Nicox Ophthalmics, Inc. (Nicox) developed a novel formulation and route of delivery consisting of applying NCX 4251 directly to the eyelids designed to minimize the intraocular exposure to fluticasone.

The safety and tolerability of NCX 4251 (fluticasone propionate nanocrystal) ophthalmic suspension, 0.1% in subjects with an acute exacerbation of blepharitis and signs and symptoms of dry eye disease was evaluated in a multi-center, randomized, double-masked, placebo-controlled, two-cohort, phase 2 study (NCX-4251-01). In Cohort 1 of the study, 15 subjects with ongoing active signs and symptoms of blepharitis evidenced by elevated eyelid discomfort, eyelid redness and eyelid debris accompanied by concurrent signs and symptoms of dry eye were randomized to NCX 4251 ophthalmic suspension 0.1% or placebo (2:1 ratio, 10 subjects on NCX 4251 and 5 subjects on placebo). Subjects additionally performed daily eyelid scrubs with baby shampoo and were treated QD for 14 days, followed by a 14-day eyelid scrubs only safety follow-up period. In Cohort 2, 21 subjects were randomized to NCX 4251 Ophthalmic Suspension 0.1% BID or placebo BID (1:1 ratio) and performed daily lid scrubs with baby shampoo and were treated for 14 days, followed by a 14-day eyelid scrubs only safety follow-up period. The interim analysis performed on Cohort 1 indicated that NCX 4251 and the new route of administration were well tolerated, and that no clinically relevant IOP elevations were observed in the study. Although the study was not powered for efficacy, changes of magnitude of clinical relevance were observed in signs and symptoms of blepharitis and dry eye. [redacted]

Blepharitis, a chronic inflammatory condition of the eyelid margin, is one of the most common ocular disorders seen by ophthalmic practitioners and is recognized to have a significant impact on ocular comfort and quality of life (Buchholz, 2006; Duncan, 2015). It often has a chronic manifestation with intermittent exacerbations defined by an increase in symptoms. Signs and symptoms of blepharitis include burning, itchiness, gritty feeling in the eyes, contact lens intolerance, photophobia, redness (telangiectasia), swelling, discomfort and crusting of the eyelid margins (Lindsley et al, 2012). While generally not sight-threatening, blepharitis can induce permanent eyelid margin alterations (eyelid notching and scarring, loss of eyelashes, in-turning of eyelashes) and even vision loss from superficial keratopathy, corneal neovascularization, or ulceration. Chronic blepharitis can also lead to destruction of the meibomian gland architecture and closure of the orifices by scar tissue (AAO PPP, 2013; Foulks, 2009). Blepharitis affects all ages and ethnic groups. While children can develop blepharitis, onset is typically during middle age. Although blepharitis is commonly

encountered in clinical practice, its true incidence and prevalence in the general population has not been well documented apart from some regional studies. In one survey, ophthalmologists and optometrists in the United States reported that 37% to 47% of their patients had evidence of blepharitis (AAO PPP, 2013; Lemp, 2009).

Even though the treatment of chronic blepharitis remains controversial, palpebral neutral shampoo cleaning has been the most widely accepted medical therapy in the US, followed by the use of antibiotic, or combination of antibiotic and steroid ointments. Short courses of topical steroids have been found beneficial for symptomatic relief in cases with clinically significant ocular inflammation in acute exacerbations of all forms of blepharitis (Lindsley et al, 2012; AAO PPP, 2013; Arrua, 2015; Pflugfelder, 2014; Jackson, 2008). Topical ocular corticosteroids, including 0.5% loteprednol etabonate and 0.1% dexamethasone, in combination with topical ocular antibiotics, have been effective in reducing the signs of blepharitis, with some differences in safety profile with respect to intraocular pressure (IOP; Pflugfelder, 2014; Hosseini et al, 2016; Comstock et al, 2017). No clinical trials have evaluated topical ocular steroids applied directly to the eyelid margin; the site of blepharitis. Eyelid margin application may avoid ocular side effects of topical ocular corticosteroids, including IOP elevation. Although fluticasone propionate (FP) demonstrates greater activity than other corticosteroids of similar potency in vasoconstrictor assays in humans, FP used in the treatment of inhalation, intranasal or dermatological disorders demonstrates low potential to cause significant suppression of the hypothalamic-pituitary-adrenal (HPA) axis (Spencer and Wiseman, 1997; Johnson, 1998; Korting and Schöllmann, 2012).

FP is a synthetic tri-fluorinated corticosteroid of medium potency (class III) with high affinity for the glucocorticoid receptor, high lipophilicity, rapid hepatic biotransformation and a favorable benefit/risk ratio (Johnson, 1998; Korting and Schöllmann, 2012). Like other topical dermal corticosteroids, FP has anti-inflammatory, immunosuppressive, antipruritic, and antiproliferative effects, which is thought to be its primary mechanism of action in the treatment of several skin disorders (Roeder et al, 2005; Cutivate Lotion US Prescribing Information, 2015). FP is a locally active glucocorticoid which has no demonstrable systemic side-effects when given by the oral or topical routes, as it appears to be extracted totally during its 'first pass' from the gut through the liver. FP has an established nonclinical and clinical safety profile as inhalation, nasal, and dermal formulations. FP is marketed for the treatment of asthma (Flovent® HFA, NDA 021433, Advair® DISKUS®, NDA 021077), rhinitis (Flonase® NDA 020121), and atopic dermatitis (Cutivate®, NDA 021152).

Nicox is developing NCX 4251 for the treatment of acute exacerbations of blepharitis to address the current unmet medical need.

1.2 Study Background

Nonclinical and Clinical Studies of NCX 4251
A summary of all nonclinical studies and the first-in-human clinical study performed with NCX 4251 can be found in the Investigator Brochure.

Description of the Study Medication
The study medication is a sterile, isotonic, buffered ophthalmic aqueous suspension containing NCX 4251 (fluticasone propionate nanocrystals) 0.1%. For further detail see Section 6.1.

Description of the Placebo Comparator
The placebo comparator is the vehicle of NCX 4251 Ophthalmic Suspension, 0.1%. For further detail see Section 6.1.

Justification of the Study Design
The proposed study is a multi-center, randomized, double-masked, placebo-controlled, Phase 2b study evaluating the safety and efficacy of NCX 4251 (fluticasone propionate nanocrystals) Ophthalmic Suspension, 0.1% QD for the treatment of acute exacerbations of blepharitis.

The study design is the same as that used during the QD-dosing cohort of NCX-4251-01.

Justification of the Route of Delivery
A reduction in the unwanted, systemic effects of glucocorticoids can be achieved by local administration to the site of action. Fluticasone propionate is a potent, locally active glucocorticoid which has been administered safely as an intranasal spray, inhaled suspension and skin formulations for decades. It is therefore most appropriate to use topical local applications of fluticasone propionate in the indication of blepharitis. A dosing paradigm has been developed by Nicox in order to apply NCX 4251 with an applicator directly at the site of the signs and symptoms of blepharitis, namely on the upper and lower eyelids as well as on the lower eyelid margin.

Justification of the Dose Selection for NCX 4251 Ophthalmic Suspension
Traditionally blepharitis has been treated by topical ocular steroids such as dexamethasone 0.1% or loteprednol etabonate 0.5%. However, this route of administration results in a minimal dose being delivered to the site of the disease origin, the margin of the eyelid. With NCX 4251, the drug will be delivered directly to the site of the disorder. The starting dose was selected based on the combination of NCX 4251 potency compared to commonly used ophthalmic steroids and optimized target delivery to the eyelid margin.

[redacted] Based on similar efficacy but a higher incidence of adverse reactions with BID dosing, QD dosing has been selected for future development.

Justification of the Placebo Control
As there is currently no FDA-approved therapy specifically indicated for blepharitis and lack of efficacious standard of care, the use of a placebo control is justified. The placebo formulation is the vehicle of NCX 4251 Ophthalmic Suspension.

Selection of the Study Population
A total of approximately 200 male and female adults with a documented history of blepharitis for at least 6 months and who are currently experiencing an acute exacerbation of blepharitis in both eyes will be randomized in this clinical study conducted in the U.S.

1.3 Potential Risks and Benefits to Human Subjects

1.3.1 Results of NCX-4251-01

To date, the safety and efficacy of NCX 4251 (fluticasone propionate) Ophthalmic Suspension has been evaluated in one dose-escalation Phase 2 trial (NCX-4251-01) in which 10 subjects received NCX 4251 0.1% QD, 5 subjects received placebo QD, 10 subjects received NCX 4251 0.1% BID, and 11 subjects received placebo BID. The results of NCX-4251-01 indicated that efficacy in reducing the signs and symptoms of blepharitis (i.e., lid debris, eyelid redness, eyelid discomfort) and in temporarily relieving the signs and symptoms of dry eye disease were not enhanced with BID application of NCX 4251 relative to QD application; however, the proportion of subjects experiencing ocular adverse events was increased with BID application.

1.3.1 Risks Associated with Other Ophthalmic or Topical Dermal Steroids

As with other ophthalmic steroids, adverse reactions with NCX 4251 (fluticasone propionate) Ophthalmic Suspension may include elevated IOP, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera (McGhee et al, 2002).

These same risks pertain to NCX 4251 (fluticasone propionate) Ophthalmic Suspension which will be applied to the eyelid margins. Specifically, raised IOP and glaucoma have been associated with use of periorbital corticosteroids for dermatological conditions such as blepharitis and eczema (Garrot and Walland, 2004; Cubey 1976).

Local adverse reactions which have been reported infrequently with topical (dermal) corticosteroids, and which may occur more frequently with higher potency corticosteroids include irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria (Fluticasone propionate cream USP 0.05% US Prescribing Information, 2016). The penetration of 0.005% fluticasone propionate ointment through eyelid skin after a single application in vitro has been shown to be very small (Tan, 2001).

Additionally, systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. However, in patients as young as 3 months, fluticasone propionate 0.05% lotion was shown to

have no effect on HPA axis function and did not cause skin thinning even when used extensively over widespread, severe inflammatory disease (Herbert, 2006).

Specific risks associated with topical ophthalmic products
There have been reports of bacterial infections associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients touching the tip of the bottles.

Benefits
Glucocorticoids produce a number of beneficial effects on the events involved in inflammation. These include inhibition of production of interleukins, inhibition of cellular and protein extravasation, inhibition of arachidonic acid generation from phospholipids and a reduction in the release of proteases and other enzymes from a number of cell types. The effects are cumulative, such that clinical improvement continues over several days or weeks of treatment (Harding, 1990). The expected benefits of the application of NCX 4251 Ophthalmic Suspension in subjects with blepharitis are the relief of the signs and symptoms of blepharitis such as eyelid redness, ocular discomfort, itchy eyes, swollen eyes, crusted eyelashes upon awakening, watery eyes, gritty, burning or stinging sensation in the eyes.

For further information, please refer to the Investigator's Brochure for NCX 4251.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The objective of this clinical study is to evaluate the safety and efficacy of NCX 4251 Ophthalmic Suspension, 0.1% vs. placebo for the treatment of the signs and symptoms of an acute exacerbation of blepharitis.

2.2 Study Endpoints

The following endpoints will be collected in the course of the study:

- Signs and symptoms of blepharitis (Eyelid Debris, Eyelid Margin Redness and Eyelid Discomfort)
- Eye Dryness using the Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Corneal [redacted] Staining (Fluorescein [redacted]
- [redacted]
- [redacted]
- Ocular signs (as assessed by slit-lamp biomicroscopy)
- IOP
- Fundus assessments
- BCVA
- AEs

2.3 Efficacy Evaluations

Primary Efficacy Endpoint

- Proportion of subjects with Complete Cure (Score 0) in each of the following: Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at the Day 15 Visit.

Secondary Efficacy Endpoint

- Mean change from baseline in the Eye Dryness Symptoms using the VAS at the Day 15 Visit;
- Mean change from baseline in Fluorescein Staining of the inferior cornea at the Day 15 Visit.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.4 Safety Evaluations

- The incidence of treatment emergent ocular and systemic AEs;
- BCVA, IOP, ocular signs (as assessed by slit lamp biomicroscopy), and fundus assessments.

2.5 Review of Safety Data by Medical Monitor

A review of the ocular and systemic safety data from each subject will be performed on an ongoing basis by the Medical Monitor. A subject may be discontinued from the study at any time for safety-related reasons at the discretion of the Principal Investigator, and/or a joint decision of the Medical Monitor and Sponsor, or for the reasons referenced in but not limited to Section 8.3.

3. STUDY DESIGN

3.1 Overall Study Design

This is a multi-center, randomized, double-masked, placebo-controlled, Phase 2b study.

Subjects will be assessed for initial eligibility at the Screening Visit (Day -14 to -7). Eligible adult subjects with a documented history of blepharitis and who are experiencing an acute exacerbation of blepharitis defined as a minimum score of '1' (on a 4-point scale) for each of Eyelid Margin Redness, Eyelid Debris, and overall Eyelid Discomfort [redacted] at both the Screening and Baseline/Day 1 Visits may be randomized into the study.

A total of approximately 300 subjects will be screened such that 200 eligible subjects will be randomized in a 1:1 ratio to receive NCX 4251 Ophthalmic Suspension, 0.1% or placebo for both eyelids, QD.

[redacted] ≥ 50 [redacted]

Study medication will be applied via a sterile applicator to the upper and lower eyelids and lower eyelid margin of both eyes once daily in the morning for 14 days. Subjects will also perform daily scrubs of the upper and lower eyelids of both eyes using diluted baby shampoo on a cotton swab prior to the application of the study medication.

Study visits will be as follows: Screening (Day -14 to -7), Baseline/Day 1, Day 4 (± 1 day), Day 8 (± 1 day), Day 11 (± 1 day), Day 15 (- 1 day), and Day 29/Exit (± 2 days; follow up visit).

Following the Screening Visit and prior to Baseline/Day 1 Visit, subjects will continue their previous routine for cleaning of eyelids that they were using prior to the Screening Visit. Both eyes will be treated from the Baseline/Day 1 Visit through the day prior to the Day 15 Visit. [redacted]. From the Day 15 Visit through the day prior to the Day 29/Exit Visit, subjects will continue performing the eyelid scrubs.

Study medication will be self-administered topically in the morning. Morning eyelid scrubs and morning study medication application will be performed by the subject at the clinical site on the days of study visits.

A subject will be considered as having completed the study after completion of Day 29/Exit Visit (± 2 days). The duration of subject participation (from the Screening Visit to the Exit Visit) is approximately 6 weeks. The overall study duration is estimated to be approximately 12 months from the first subject enrolled until completion of the last subject.

4. SUBJECT SELECTION

4.1 Number of Subjects and Sites

This study will be conducted at approximately 5 to 10 sites in the U.S. Additional sites may be added based on enrollment rates. Overall, approximately 300 subjects will be screened and 200 subjects will be randomized into the study.

4.2 Subject Population Characteristics

The target population in this study will be adult men and women with a documented history of blepharitis for at least 6 months and who are experiencing an acute exacerbation of blepharitis.

4.3 Inclusion Criteria

Prior to inclusion in the study, each subject must fulfill all of the following criteria:

1) be at least 18 years of age;
2) have a documented history of blepharitis of at least 6 months;
3) be currently experiencing signs and symptoms of blepharitis defined as a minimum score of '1' for each of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort [redacted] at both the Screening and Baseline/Day 1 Visits.
4) have a Best Corrected Visual Acuity (BCVA) of +0.60 logMAR (approximately 20/80 Snellen) or better in each eye as measured using an ETDRS chart with the subject wearing their habitual correction or with pinhole refraction;
5) be able to perform eyelid scrubs with diluted baby shampoo and apply study medication satisfactorily, in the opinion of the Investigator;
6) if female, must either be incapable of pregnancy because of hysterectomy, bilateral tubal ligation, or bilateral oophorectomy, or be post-menopausal (have been amenorrheic for at least 2 years) or must use an effective method of birth control for the duration of the study. Female subjects of childbearing potential must have a negative urine pregnancy test and not be breastfeeding or planning a pregnancy;
7) be able to provide written informed consent and sign the HIPAA form to participate in the study, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local regulations, before initiating any study-related procedures; and
8) be able and willing to comply with treatment and all study procedures

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1) have an Eyelid Debris score of 3 or have cylindrical collarettes in either eye;
2) have clinically significant abnormality of the eyelids or lashes (e.g., entropion, ectropion) other than blepharitis, or have a history of lagophthalmos or trichiasis; or have had eyelid surgery (including blepharoplasty) within 4 years of the Screening Visit. Eyelid surgery performed >4 years prior to the Screening Visit is permitted provided there is normal apposition of the eyelids upon closure and that there is no

residual lagophthalmos, no distortion of the lid margin and no abnormal lid function resulting in potentially increased exposure of the ocular surface;

3) have received an injection of Botulinum toxin (Botox or equivalent) in the periocular area within 3 months prior to the Screening Visit;
4) have any current or recurrent ocular infections (bacterial, viral or fungal), active ocular inflammation other than blepharitis or dry eye (i.e., follicular conjunctivitis, iritis) or preauricular lymphadenopathy;
5) have current or recurrent diagnosis of ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis (e.g., confluent epithelial loss or any infiltrates);
6) have been diagnosed with glaucoma or ocular hypertension, or have an IOP > 21 mmHg at the Screening Visit or Baseline/Day 1 Visit;
7) have a history of IOP elevation with steroid use (i.e., steroid responder);
8) unable or unwilling to discontinue the use of contact lenses from Screening to Day 29/Exit Visit;
9) use any eye makeup (including on the eyelids, eyelid margins, and lashes) at the Screening Visit and unwilling to cease the use of eye make-up up to the Day 15 Visit;
10) cosmetic eyelash procedures (e.g., eyelash curling) from the Screening Visit up to the Day 15 Visit, or a history of permanent/semi-permanent eye make-up procedure (e.g., eyelash extensions / false eyelashes, eyelash tinting, eyeliner tattooing) within 30 days of the Screening Visit or planned procedure during the study period;
11) have permanent punctal plugs or history of nasolacrimal obstruction;
12) have a history of ocular surgical intervention within 6 months prior to the Screening Visit or any planned ocular procedure during the study period;
13) have known hypersensitivity to fluticasone propionate, to any other component of the study medication, or to ophthalmic diagnostic dyes [redacted]
14) use strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin);
15) unable or unwilling to discontinue use of any non-diagnostic ophthalmic treatments (topical, intraocular or systemic) including topical autologous serum eyedrops, artificial tears and ocular lubricants. Subjects should not have used artificial tears or ocular lubricants for at least 24 hours prior to the Screening Visit, and for at least 30 days for all other ophthalmic medications;
16) unable or unwilling to discontinue use of any non-diagnostic ophthalmic procedures [redacted] from the Screening Visit through the study period. Warm compresses and the subject's standard of care eyelid scrubs are permitted from the Screening Visit through the evening prior to Baseline/Day 1 Visit, and protocol-specified eyelid scrubs from Baseline/Day 1 through the study period;
17) have a history of meibomian gland probing within 3 months prior to the Screening Visit;

18) use of any corticosteroid agent or anabolic steroid within 30 days of the Screening Visit or during the study treatment period;
19) use of isotretinoin or any other retinoids within 12 months of the Screening Visit;
20) have any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, diabetes, cystic fibrosis) in the opinion of the Investigator;
21) have thyroid ophthalmopathy, rosacea or seborrheic dermatitis;
22) have any auto-immune disease (e.g., rheumatoid arthritis, lupus, Sjögren's, graft-versus-host disease (GVHD)). Note: Patients with controlled, mild rheumatoid arthritis without any other component (e.g., psoriatic) are allowed to be included in the study;
23) have a condition which, in the Investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation or their ability to perform eyelid scrubs and apply the study medication;
24) have participated in any drug or device study within 30 days prior to the Screening Visit and/or planning to participate in any other study while participating in the current study; and
25) were randomized in the NCX-4251-01 clinical trial.

5. CONCOMITANT MEDICATION(S)

5.1 Previous and Concomitant Medication(s)

All non-ophthalmic medications used in the 3 months prior to the Screening Visit and all ophthalmic medications used in the 12 months prior to the Screening Visit must be recorded. Additionally, all medications used between the Screening Visit and the Day 29/Exit Visit must be recorded.

Any diagnostic ophthalmic agents administered throughout the study will not be captured in the concomitant medication log.

5.2 Prohibited Medication(s) and Procedures

All the prohibited drugs and procedures mentioned below are also listed in Section 4.4 ("Exclusion Criteria").

From the Screening Visit through the Day 29/Exit Visit subjects must not receive:

- any non-diagnostic ophthalmic treatments (topical, intraocular or systemic) including topical autologous serum eyedrops, artificial tears, ocular lubricants, or procedures [redacted] other than the eyelid scrubs administered in this trial (note: warm compresses and the subject's standard of care eyelid scrubs are permitted from the Screening Visit through the evening prior to Baseline/Day 1 Visit),
- strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin)
- any corticosteroid or anabolic steroid agents
- isotretinoin or any other retinoids
- topical ocular or periocular antibiotics

Medication which is considered necessary for the subject's safety may be given at the discretion of the Investigator and/or their health care provider during the study. If possible, the Medical Monitor should be consulted prior to the administration of the disallowed medication (if not possible, the Medical Monitor should be notified as soon as possible thereafter) to determine whether the subject may continue in the study.

Contact lens use is prohibited from the Screening Visit to the Day 29/Exit Visit. The use of any eye make-up (including on the eyelids, eyelid margins, and lashes) is prohibited up to the Day 15 Visit.

Additionally, cosmetic eyelash procedures (e.g. eyelash curling) are prohibited from the Screening Visit up to the Day 15 Visit, and permanent/semi-permanent eye make-up procedures (e.g., eyelash extensions / false eyelashes, eyelash tinting, eyeliner tattooing) are prohibited up to the Day 29/Exit Visit.

Additionally, the following are prohibited:

- Botulinum toxin (Botox or equivalent) injected in the periocular area within 3 months prior to the Screening Visit
- Meibomian gland probing within 3 months prior to the Screening Visit
- Permanent punctal plugs

6. STUDY SUPPLIES

6.1 Description of Study Medication

NCX 4251 Ophthalmic Suspension, 0.1% is a sterile, isotonic, buffered ophthalmic suspension containing 0.1% fluticasone propionate nanocrystals. The inactive ingredients are: [redacted]

The placebo comparator is the vehicle of NCX 4251 Ophthalmic Suspension.

6.2 Packaging of the Study Medication

NCX 4251 Ophthalmic Suspension and placebo comparator are supplied as [redacted]

Each kit is a carton that contains [redacted] The kit will be identified by a unique "kit number." The subject will be dispensed one kit after randomization at the end of the Baseline/Day 1 Visit.

All study medication will be packaged, labeled, and supplied to the site by the study medication supplier under the direction of Nicox. Each kit contains sufficient study medication for the duration of the study treatment period.

6.3 Labeling of the Study Medication

All labeling will be in English and will comply with U.S. federal regulations for investigational drug product.

The kit and bottles will be labeled with the following:

- Sponsor
- Protocol number
- Kit number
- Instructions for use
- Contents
- Storage temperature
- Cautionary statement: "*New Drug - Limited by Federal Law to Investigational Use"*

6.4 Storage of the Study Medication

It is the site's responsibility to ensure that all study medication is stored in a secure area and administered only to randomized subjects and in accordance with conditions specified in this protocol.

At the site, the study medication will be stored [redacted] in accordance with the conditions specified in the site shipment documentation.

[redacted]

The storage conditions will be indicated on the kit and bottle labeling.

6.5 Accountability of Study Medication

It is the responsibility of the site to maintain detailed study medication accountability records.

The study medication will be shipped by the study medication supplier to each study site. The receipt of study medication by the site should be documented. The dispensed and returned study medication will be recorded by the site on an inventory log.

The importance of returning the kit with all bottles dispensed must be emphasized to the subjects. Study medication deliberately and/or accidentally destroyed must be accounted for and the reason must be documented. Any discrepancy between dispensed and returned study medication must be explained and documented by the site.

6.6 Assigning Subjects to Treatment

Each site will be assigned a 2-digit site ID by the Sponsor or its representative. At the Screening Visit, the site will assign a unique 3-digit screening number to each subject and record it in the screening log. The site will then assign the subject a unique consecutive Subject ID comprised of the 2-digit site ID followed by the 3-digit screening number.

Subjects must meet all qualification criteria prior to randomization at the Baseline/Day 1 Visit. Approximately 100 subjects will be randomly assigned to NCX 4251 0.1% and approximately 100 subjects will be randomized to placebo in a 1:1 ratio.

[redacted] ≥ 50 [redacted]

Subjects will be assigned a randomization number available at that site. No randomization numbers will be skipped or omitted. Randomization numbers will be unique across the sites and will correspond with a kit number.

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons.

The subjects, investigators, the Sponsor, the Medical Monitor, and the CRO personnel interacting with the clinical sites (or handling study data) will be masked to the treatment assignment. During study visits Investigators, the Sponsor, the Medical Monitor, and masked CRO personnel interacting with the clinical sites must not be present during the instruction and supervision of study medication application. Instruction and supervision of subjects on the application of study medication will be performed by unmasked site personnel who will not perform any other study assessments.

6.7 Emergency Subject Unmasking

If unmasking of a subject becomes critical to the subject's safety, the Principal Investigator must authorize such decision. If possible, such decision must be first consulted with both the study Sponsor and the Medical Monitor. The Sponsor and the Medical Monitor must be notified within 24 hours following an emergency unmasking of any subject.

6.8 Study Medication Dispensing and Collection

For each subject fulfilling eligibility criteria, the clinical site staff will randomize subjects as per the randomization schedule [redacted] prior to the start of the study. A randomization number, which corresponds to a study medication kit number, will be allocated to each subject. The study medication kit number corresponds to a unique box containing [redacted]. The randomization and the study medication kit number must be allocated only on the day of the first treatment application during Baseline/Day 1. Replacement kit numbers will be provided should a dispensed kit become lost or damaged.

Once all Baseline/Day 1 Visit study procedures have been completed, the site will dispense the study medication to the subject. Each subject will be given one kit containing [redacted]

Study medication will be dispensed by the site designee (other than the investigator(s)) at the study site.

Subjects will be instructed to return their study medication [redacted] to the Study Coordinator or another designated individual at the Day 15 Visit. An inventory will be conducted by the site.

Each subject will be given a copy of the study medication dosing and storage instructions.

6.9 Instructions for Eyelid Scrubs

The eyelid scrub procedure must be performed by the subject, prior to the study medication application, on both eyes each morning [redacted]

On study visit days, the subject must not perform eyelid scrubs at home; rather, eyelid scrubs will be performed at the site by the subject under the instruction and supervision of unmasked site study staff. Study staff will contact the subject the day prior to a scheduled visit to instruct the subject not to perform eyelid scrubs the morning of their visit and to bring their study supplies to the visit.

Subjects must perform the eyelid scrubs as instructed using the supplies provided by the study site. Each subject will be given a copy of the eyelid scrub instructions.

6.10 Instructions for Use and Application of Study Medication

The study medication must be administered to both eyelids each morning, [redacted] from the Baseline/Day 1 Visit to the day prior to the Day 15 Visit. The first study medication application (Baseline/Day 1 Visit) will be performed at the site by the subject under the instructions and supervision of site study staff. Similarly, at the Day 4, 8, and 11 Visits, application of the study medication will also be performed at the site by the subject under the supervision of site study staff. Study staff will contact the subject the day prior to a scheduled visit to instruct the subject not to apply study medication the morning of their visit and to bring their study medication and study supplies to the visit.

Subjects must apply the study medication as instructed using the supplies provided by the study site.

6.11 Compliance with Eyelid Scrubs and Study Medication

It is important to encourage the subject to be compliant with eyelid scrubs and application of study medication. Compliance of both will be captured in a subject diary. The subject will be instructed on diary completion.

6.12 Return of Study Medication by the Clinical Sites

Return of used and unused study medication by the clinical site to the study medication supplier should be performed following the completion of the last subject last visit at the site, and only after database lock and following onsite verification by the CRA.

6.13 Other Study Supplies

Sites will also be provided with:

- Sterile applicators and tubes (for study medication)
- Baby shampoo, cotton swabs, bottled water, tissues, and capped tubes (for eyelid scrubs)
- Safety scissors (for opening tube packaging)
- Subject diaries and dosing instructions
- Early Treatment Diabetic Retinopathy Study (ETDRS) charts and/or illuminator cabinet (or replacement bulb with diffuser), if needed
- Urine pregnancy tests
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- VAS rulers

Additional supplies may be provided once discussed and approved by the Sponsor.

7. STUDY PROCEDURES BY VISIT

The following sections provide a list of procedures and assessments for each study visit as outlined in the Times and Events Schedule (Appendix 1). Refer to Appendix 2 for information on the methods of clinical evaluation. With the exception of the Screening Visit, which may be performed at any time of the day, all study visits will be conducted in the morning. Ocular examination procedures will be performed bilaterally, and in the order listed for each visit.

7.1 Screening Visit (Day -14 to -7)

Prior to any study assessments, potential subjects will be identified and the Investigator (or designee) will conduct the informed consent process. The purpose of the study, the study methods (visits and assessments), risks/benefits, and subject responsibilities will be discussed. The subject's willingness and ability to participate in the study will be assessed. If the subject chooses to proceed with study participation, written informed consent and HIPAA authorization will be obtained as appropriate for local privacy regulations. The original signed document will be retained in the subject records and a copy will be provided to the subject.

Perform the following procedures and/or collect the following information in the order listed:

- Assign the screening number and record in the screening log
- Record any AEs from the time the subject signs the ICF
- Record demographic data
- Record past and current relevant medical and ophthalmic history, including previous surgery(ies)/procedure(s)
- Record current (within 30 days) use and frequency of subject's routine care for blepharitis (e.g. eyelid scrubs, warm compresses)
- Record prior (past 12 months for isotretinoin or any other retinoids, past 3 months for other non-ophthalmic, and past 12 months for ophthalmic medications including over-the-counter products) and concomitant medication(s)
- Perform urine pregnancy test (for females of childbearing potential)
- Assess Eye Dryness using the VAS [redacted]
- Measure BCVA
- Perform eyelid evaluation [redacted] (Eyelid Discomfort, followed by Eyelid Margin Redness and Eyelid Debris)
- Perform slit lamp biomicroscopy [redacted]
- [redacted]
- Assess Fluorescein Staining [redacted]
- [redacted]
- Measure IOP

- [redacted]
- Perform dilated ophthalmoscopy

*Instruct the subject that they should continue with their standard routine of warm compresses and/or routine eyelid scrubs **until the day before the Baseline/Day 1 Visit.** Subjects **must not** perform any eyelid scrubs on the morning of the next visit, Baseline/Day 1, regardless of their standard routine.*

At all visits following the signature of the ICF at the Screening Visit, adverse events and changes in concomitant medications and procedures will be captured.

7.2 Baseline/Day 1 Visit

The visit will occur 7 to 14 days after the Screening Visit. At all visits at which it is required, eyelid scrubs and study medication application will be performed by the subject under the instruction and supervision of the site staff. Perform the following procedures and/or collect the following information in the order listed:

- Medical/Medication History Update
- Assess Eye Dryness using the VAS [redacted]
- Measure BCVA
- Perform eyelid evaluation [redacted] (Eyelid Discomfort, followed by Eyelid Margin Redness and Eyelid Debris) [redacted]
- Perform slit lamp biomicroscopy [redacted]
- [redacted]
- Assess Fluorescein Staining [redacted]
- [redacted]
- Measure IOP
- [redacted]
- Instruct the subject on the proper eyelid scrub technique
- Supervise the subject as they perform eyelid scrubs
- Review inclusion/exclusion criteria and determine eligibility
- Randomize eligible subjects
- Dispense study medication and additional eyelid scrub supplies
- Instruct/supervise the subject as they apply study medication
- Record adverse events
- Dispense subject diary and subject dosing instructions

Instruct the subject to perform eyelid scrubs each morning [redacted]

However, instruct the subject to not perform eyelid scrubs or apply study medication on the morning of the next visit. Subjects must bring their study medication and study supplies to all visits.

At all subsequent visits, if the subject has performed eyelid scrubs and/or applied study medication the morning of the visit, the subject must not be evaluated that day, and should be rescheduled the next day or as soon as possible. Please consult the Sponsor or CRO for additional guidance.

7.3 Day 4 (± 1 day) Visit

Perform the following procedures and/or collect the following information in the order listed Eyelid scrubs and study medication application must be performed by the subject under the supervision of the study staff. The visit will occur 4 days (± 1 day) after the Baseline Visit:

- Medical/Medication History Update
- Measure BCVA
- Perform eyelid evaluation [redacted] (Eyelid Discomfort followed by Eyelid Margin Redness and Eyelid Debris) [redacted]
- Perform slit lamp biomicroscopy [redacted]
- Measure IOP
- Supervise the subject as they perform eyelid scrubs
- Supervise the subject as they apply study medication [redacted]
- Review the subject diary for compliance
- Record adverse events

Instruct the subject to perform eyelid scrubs each morning [redacted]*. However, instruct the subject to not perform eyelid scrubs or apply study medication on the morning of the next visits. Subjects must bring their study medication to the visits. Contact the subject the day before the next visits to remind them of these requirements.*

7.4 Day 8 (± 1 day) and Day 11 (± 1 day) Visits

Perform the following procedures and/or collect the following information in the order listed. Eyelid scrubs and study medication application must be performed by the subject under the supervision of the study staff.

- Medical/Medication History Update
- Assess Eye Dryness using the VAS [redacted]

- Measure BCVA
- Perform eyelid evaluation [redacted] (Eyelid Discomfort, followed by Eyelid Margin Redness and Eyelid Debris and) [redacted]
- Perform slit lamp biomicroscopy [redacted]
- [redacted]
- Assess Fluorescein Staining [redacted]
- [redacted]
- Measure IOP
- Supervise the subject as they perform eyelid scrubs
- Supervise the subject as they apply study medication [redacted]
- Review the subject diary for compliance
- Record adverse events

Instruct the subject to perform eyelid scrubs each morning [redacted] *However, instruct the subject to not perform eyelid scrubs or apply study medication on the morning of the next visit. Subjects must bring their study medication to the visit. Contact the subjects the day before the next visit (Day 15) to remind them of these requirements.*

7.5 Day 15 (- 1 day) Visit

Perform the following procedures and/or collect the following information in the order listed. Eyelid scrubs must be performed by the subject under the supervision of the study staff.

- Medical/Medication History Update
- Perform urine pregnancy test for females of childbearing potential
- Assess Eye Dryness using the VAS [redacted]
- Measure BCVA
- Perform eyelid evaluation [redacted] (Eyelid Discomfort, followed by Eyelid Margin Redness and Eyelid Debris) [redacted]
- Perform slit lamp biomicroscopy [redacted]
- [redacted]
- Assess Fluorescein Staining [redacted]
- [redacted]

- Measure IOP
- [redacted]
- Supervise the subject as they perform eyelid scrubs
- Review the subject diary for compliance and collect it
- Collect used and unused study medication
- Record adverse events

Instruct the subject to continue to perform eyelid scrubs every morning except on the morning of the next visit (Day 29/Exit Visit). Additionally, instruct the subject to refrain from wearing contact lenses until they have completed the Day 29/Exit Visit.

7.6 Day 29 (± 2 days)/Exit Visit

Perform the following procedures and/or collect the following information in the order listed.

- Medical/Medication History Update
- Assess Eye Dryness using the VAS [redacted]
- Measure BCVA
- Perform eyelid evaluation [redacted] (Eyelid Discomfort, followed by Eyelid Margin Redness and Eyelid Debris) [redacted]
- Perform slit lamp biomicroscopy [redacted]
- [redacted]
- Assess Fluorescein Staining [redacted]
- [redacted]
- Measure IOP
- Supervise the subject as they perform eyelid scrubs
- Perform dilated ophthalmoscopy
- Record adverse events
- Utilize EDC to exit the subject

7.7 Unscheduled Visits

Additional examinations or analyses may be performed as necessary to ensure the safety of subjects during the study period. Each unscheduled visit will be documented with results of the following assessments, as appropriate:

- Adverse event(s) and concomitant medication(s) (if applicable)
- Assess Eye Dryness using the VAS [redacted]

- BCVA
- Eyelid evaluation [redacted] (Eyelid Discomfort, followed by Eyelid Margin Redness and Eyelid Debris)
- Slit lamp biomicroscopy
- IOP

The Investigator may perform any other examination that is regarded as appropriate.

8. SCREEN FAILURES, COMPLETION AND DISCONTINUATION

8.1 Subject Screen or Eligibility Failures

Subjects who are screen or randomization failures should not be randomized into the study. The reason for screen/randomization failure must be documented.

8.2 Subject Completion

A subject is considered to have completed the study at the end of the Day 29/Exit Visit.

8.3 Subject Early Discontinuation

A subject may be discontinued from the study prior to the final study visit at the discretion of the Investigator, Sponsor, and/or IRB. Subjects may also discontinue their participation in the study at any time for any reason of their choosing.

A subject <u>may</u> be discontinued from the study for the following reasons, including but not limited to:

- Serious adverse event
- Violation of eligibility criteria
- Lack of compliance with the study procedures

A subject must be discontinued from the study for the following reasons, including but not limited to:

- If IOP > 36 mmHg in the same eye at two consecutive visits during the Treatment Period
- Withdrawal of consent
- Subject becoming pregnant in the course of the study
- Eye infection

Procedures for Discontinuation

If a subject is discontinued or withdraws consent, no procedures other than those which may be related to the follow-up of AEs will be required. The Investigator will document the reason for the subject withdrawal.

If a subject withdraws their consent during the 14-day Treatment Period, all efforts should be taken to complete the Day 15 Visit procedures prior to subject's exit.

If a subject is discontinued due to an AE, the status of the AE at the time of discontinuation must be documented.

For any subject that is discontinued due to an AE the Investigator must ensure that adequate medical care/treatment will be provided.

8.4 Subject Lost to Follow-up

Subjects who fail to present for a study visit should be contacted in an attempt to have the subject comply with the protocol and to return the diary and study medication, if applicable. If

a subject cannot be contacted with a minimum of three documented telephone calls followed by a certified letter and there is no known reason for withdrawal (e.g., withdrawal of consent), the reason for withdrawal from the study will be recorded as “lost to follow-up”. The date of withdrawal will be considered as seven days after the certified letter was mailed.

8.5 Study Termination

Investigators and subjects should understand that the study may be discontinued by the Sponsor (Nicox) at any time, without their consent.

9. PROTOCOL COMPLIANCE

Subjects who experience major protocol deviations will have all their data excluded from the Per Protocol (PP) analysis. The list of major protocol deviations, as well as minor protocol deviations, will be finalized prior to database lock.

In order to correctly identify and document protocol deviations, protocol deviations will be categorized as follows:

- **Minor Deviation:** Deviation considered to not impact the primary efficacy outcome of the study (i.e., does not affect the study results).
- **Major Deviation:** Deviation considered to impact the primary efficacy outcome of the study (i.e., affects the study results).

All deviations will be recorded by the site and classified by the Sponsor.

10. ADVERSE EVENTS

10.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Lack of efficacy will be reported as a treatment failure, not as an AE.

10.2 Severity of Adverse Event

The severity of an AE should be categorized as mild, moderate or severe per Investigator's judgment with the following scale in consideration:

- **Mild**: Awareness of a sign or symptom that does not interfere with the subject's usual activities or is transient, resolved without treatment and with no sequelae.
- **Moderate**: interferes with the subject's usual activities, and or requires symptomatic treatment.
- **Severe**: symptom(s) causing severe discomfort and significant impact of the subject's usual activities and requires treatment.

10.3 Causal Relationship with Study Medication

A determination of the relationship between an AE and the study medication must be made by the Investigator for each AE. The following terms to evaluate the causality of the AE with the study drug should be used:

- **Unrelated:** a simultaneous disease, a simultaneous treatment or any other known cause is clearly responsible for the safety event and the AE is not related to the study medication.
- **Unlikely:** on the basis of the available knowledge regarding the subject's history, the disease process, the timing of the safety event in relation to the application of the study medication and the mode of action of study medication, a relation between the study medication and the safety event is unlikely, but cannot be totally excluded.
- **Possible:** this relation exists when the safety event follows the reasonable chronological sequence from the moment of the study medication application, but when the safety event could also have been caused by the clinical condition of the subject or by other treatment administered to the subject.
- **Probable:** this relation exists when the safety event follows a reasonable chronological sequence from the moment of the study medication application, corresponds to a known effect of the study medication, is confirmed by the observation of an improvement upon discontinuation of the study medication application, and therefore the study medication is the most probable of all the causes.

- **Definite:** this relation exists when the safety event follows a reasonable chronological sequence from the moment of the study medication application, corresponds to a known effect of the category of the studied medication, is confirmed by the observation of an improvement upon discontinuation of the study medication, and no other reasonable cause exists.

Early exit for lack of efficacy/worsening of the disease will not be considered as an adverse event but as a treatment failure.

10.4 Serious Adverse Events

SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Results in-subject hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly/birth defect (Section 12.2 - Procedure in Case of Pregnancy), or
- Results in life-threatening illness or injury (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe, or had continued untreated).
- Results in a significant and persistent loss or impairment of vision.

Additionally, medical events that may not meet these criteria, may be considered an SAE if, based on the medical judgment of the Investigator, such medical events may require an intervention to prevent any of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided: the term "severe" is often used to describe the intensity of a specific event. This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

Elective or planned procedures requiring hospitalization will not be considered SAE’s; however, other events may occur during this hospitalization that may be considered serious or non-serious adverse events and will need to be captured according to the protocol.

10.5 Adverse Event Reporting

In this study, subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., “How has your health been since the last visit?”). If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE Form(s).

Additionally, subjects will be instructed to contact the Investigator, and/or study coordinator if any significant AEs occur between study visits.

From the signing of the ICF on the day of the Screening Visit, all AEs must be recorded on the appropriate AE form. All AEs must be reported whether or not considered causally related to study medication. For every AE, the Principal Investigator will provide an assessment of the severity and causal relationship to study medication, document all actions taken with regard to study medication, and any other treatment measures for the AE.

10.6 Serious Adverse Event Reporting

Any SAE occurring from the signing of the ICF on the day of the Screening Visit until Day 29/ Exit must immediately be reported [redacted] representing Nicox, and recorded on the appropriate forms. All subjects with an SAE must be followed up until complete healing or stabilization, or up to 30 days after the end of Treatment Period (Day 15), whichever occurs first, and the SAE outcome reported.

The Investigator must supply the company representing Nicox with any additional requested information (e.g., autopsy reports and final medical reports).

In the event of an SAE, the Investigator must:

1) Notify the Primary Contact for Study Related Matters and SAEs immediately (see contact information on Page 2 and Section 12.1), at the latest within 24 hours of becoming aware of the initial SAE. Complete an SAE Form (see instructions for completion of SAE Form in Appendix 3) and send it to the Primary Contact for Study Related Matters and SAEs. Retain all submission confirmations with the items submitted.
2) Obtain and maintain in subject's files pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3) Complete and submit further follow-up reports for data collected until the SAE has resolved or a decision for no further follow up has been taken.
4) Promptly inform the local IRB and/or other applicable regulatory body as required by local regulations.

11. STATISTICAL CONSIDERATIONS AND METHODS OF ANALYSIS

An analysis plan containing detailed statistical methods, including accounting for missing data, will be generated and finalized prior to database lock.

11.1 Determination of Sample Size and Power Calculations

The primary objective of this study is to demonstrate that the proportion of subjects with complete cure (score =0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at Day 15 for NCX 4251 treated subjects is statistically superior to placebo treated subjects using a 2-sided alpha = 0.05.

For the complete cure endpoint, [redacted] approximately 208 subjects randomized overall (~104 subjects randomized per treatment group, with 94 subjects per treatment group completing the Day 15 study time point evaluations) [redacted] to demonstrate statistical superiority to placebo.

The above analysis assumed a Day 15 time point; [redacted]; and a two-sided significance level of 5% using a Fisher's exact test.

The secondary objective of this study is to demonstrate that mean reduction from baseline in Eye Dryness evaluated on VAS and/or Fluorescein Staining of inferior cornea at Day 15 for NCX 4251 are statistically superior to placebo using a Hochberg procedure to maintain the overall Type I Error rate = 0.05.

For Eye Dryness endpoint, [redacted] approximately 124 subjects randomized overall (~62 subjects per treatment group, with 55 subjects per group completing Day 15) [redacted] to demonstrate statistical superiority to placebo.

The above analysis assumed a Day 15 time point; [redacted] and a two-sided significance level of 0.025 using a two-sample t-test.

For Fluorescein Staining of inferior cornea, [redacted], approximately 72 subjects randomized overall (~36 subjects per treatment group, with 32 subjects per group completing Day 15) [redacted] to demonstrate statistical superiority to placebo.

The above analysis assumed a Day 15 time point; [redacted] and a two-sided significance level of 0.025 using a two-sample t-test.

The study will be considered a success and NCX 4251 will be claimed to be superior to placebo in the proportion of subjects with complete cure (score =0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at Day 15 if the primary endpoint is demonstrated to be statistically significant in favor of NCX 4251.

Statistical inference will be made on the two secondary endpoints only if the primary endpoint demonstrates statistical significance in favor of NCX 4251. Multiplicity correction within the two secondary efficacy endpoints will be completed using Hochberg's procedure.

[redacted]

11.2 Analysis Population

- Intent-to-Treat Population: The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.
- Per-Protocol Population: The per-protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations likely to seriously affect the efficacy measures of the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.
- Safety Population: The safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

11.3 Data Display

Summaries for continuous variables will include the sample size, mean, standard deviation, standard error, median, minimum, and maximum. Summaries for discrete variables will include frequency counts and percentages. The Baseline measure will be defined as the last non-missing measure prior to initiation of study treatment. Analyses will be completed on the study eye and fellow eye separately. [redacted]

11.4 Collection and Derivation of Efficacy Assessments

For both eyes, eyelid signs and symptoms (Eyelid Margin Redness, Eyelid Debris, Eyelid Discomfort) will be assessed.

The primary efficacy endpoint is the complete cure (score = 0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at Day 15. The primary efficacy analyses of the primary efficacy endpoint will be conducted in the ITT population; intercurrent events handled in the following manner for each measure comprising the primary endpoint (Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort) after which complete cure will be determined:

[redacted]

[redacted]

The secondary efficacy endpoints are the mean change from baseline in Eye Dryness (VAS) and mean change from baseline in fluorescein staining of inferior cornea at Day 15. The primary analyses of the secondary efficacy endpoints will be conducted in the ITT population of subjects with an Eye Dryness VAS [redacted] ≥ 50 at the B[redacted]

[redacted]

11.5 Hypothesis and Methods of Analysis

11.5.1 Efficacy Analyses

Complete cure (score =0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort will be summarized using discrete summary statistics (frequency counts and percentages) as well as two-sided 95% Clopper-Pearson confidence intervals by treatment group. The primary efficacy analyses will test the difference in the proportion of study eyes with complete cure in the composite score between NCX 4251 Ophthalmic Suspension and placebo at Day 15 using a generalized estimating equation model with complete cure as the response, treatment as a fixed effect and baseline composite score as a covariate. The marginal proportions and difference in proportions along with the corresponding two-sided 95% Confidence Intervals (CIs) and p-value will be presented.

Secondarily, differences (NCX 4251 Ophthalmic Suspension minus placebo) between treatment groups will be summarized using difference in proportions, 95% asymptotic confidence intervals around the differences in proportions, and Pearson's chi-squared test. Summaries will be presented for the Day 15 Visit as well as each other post-baseline visit.

[redacted]

[redacted]

Secondary endpoints will be summarized using continuous summary statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) as well as two-sided 95% t-distribution confidence intervals around the mean by treatment group. The primary analysis of the secondary outcome will employ a linear model with mean change from baseline in Eye Dryness evaluated on the VAS and mean change from baseline in Fluorescein Staining of the inferior cornea at Day 15 as the response and baseline eye dryness as a covariate. Least squared means and differences between treatment groups, along with corresponding 95% CIs and p-values will be presented.

[redacted]

Detailed statistical methodology will be provided in the SAP.

11.5.2 Safety Analyses

Subject disposition, demographics, and baseline characteristics will be summarized and presented in data listings.

Safety analyses are based on the safety dataset. The safety dataset will include all subjects who receive at least one dose of study medication.

Adverse events (AEs) will be coded using the MedDRA dictionary. The safety analysis will summarize treatment emergent ocular and systemic AEs for all treated subjects, using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group.

A treatment-emergent AE (TEAE) is defined as an AE that occurred on or after the treatment was initiated. Ocular TEAEs by treatment group: NCX 4251 0.1% and placebo, will be summarized, by relationship to study drug, and by severity. Non-ocular TEAEs will be summarized by treatment group as follows: non-ocular TEAEs, by relationship to study, and by severity. Serious AEs (SAEs), AEs resulting in study drug discontinuation, and deaths will be presented in data listings.

Other ocular safety data including visual acuity, slit-lamp biomicroscopy, IOP, and dilated ophthalmoscopy will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

11.5.3 Interim Analysis

There is no interim analysis planned for this study.

12. EMERGENCY PROCEDURES

12.1 Emergency Contact Procedure

In case of any Safety Event including an SAE, the first person to contact is:

[redacted]

The secondary contact is the study Medical Monitor:

[redacted]

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. Each subject will receive the Investigator's emergency contact information (to call if needed).

12.2 Procedure in Case of Pregnancy

If a pregnancy occurs during the study, pregnancy itself is not regarded as an AE unless there is a suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication.

If a female subject becomes pregnant during the study, the subject will be withdrawn from the study immediately. However, any pregnancies must be followed up, and their outcomes must be reported to Nicox [redacted] (i.e., mother and fetus(es) must be followed up at least until the birth of the infant and one month after the birth of the infant). Follow-up will include course, duration, outcome of the pregnancy and the health of the infant, as applicable.

If the outcome of pregnancy is:

- Elective abortion without complications: it must be documented and reported to Nicox [redacted], but it should not be handled as an AE.
- Any spontaneous miscarriage or abortion for medical reasons or congenital anomaly or birth defect: it must be documented and handled as a SAE and full details will be requested.

Any complications during pregnancy must be recorded as AEs and may constitute SAEs if they fulfill any of the specified criteria for a SAE.

13. STUDY MANAGEMENT

13.1 Monitoring

Site monitoring is conducted to assess that subject protection, study procedures, study medication application, and data collection processes meet protocol, ICH, GCP, and regulatory guidelines/requirements.

Before the study starts, the Clinical Research Organization (CRO) representing Nicox will visit/call the investigational sites to:

- Determine the adequacy of the facilities,
- Discuss with the Investigator(s), and other personnel involved in the study, about their responsibilities with regard to protocol adherence, and also about Sponsor's responsibilities.

During the study, a Clinical Research Associate (CRA) [redacted] will monitor the study on a periodic basis by having regular contacts with the investigational sites, including on-site visits, to:

- Provide information and support to the Investigator(s),
- Confirm that facilities and investigational site staff remain acceptable,
- Ensure that the investigational site study team is adhering to the protocol, including verifying the accuracy of data recorded in the eCRF and that the study medication logs are being maintained.

Any detected non-compliance with the approved study protocol, GCP, or any applicable regulatory requirements will be fully documented by the CRA. During the monitoring visits, the Investigator and clinical study staff should be available for questions, verification of data from the source documentation, and possible correction to the eCRF.

Following each monitoring visit, the CRA will send the Investigator a follow up letter detailing any actions required by the investigational site staff. Any actions must, wherever possible, be addressed immediately, or by the next scheduled monitoring visit.

The CRA [redacted] will be reachable between visits if the Investigator, or other study staff at the site, needs information and advice.

13.2 Source Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP Section 4.9, and regulatory and institutional requirements for the protection of subject confidentiality.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source documents may include, but are not limited to, a subject's medical records, hospital charts if any, clinic charts if any, the Investigator's subject study files, pharmacy dispensing records, recorded data from automated instruments, as well as the results of diagnostic tests such laboratory tests.

13.3 Source Data Verification

To ensure that data in the eCRF is accurate and complete and in accordance with subject source documents and other source data, source data verification (SDV) will be performed by the monitor on eCRFs and SAE and pregnancy related documents as detailed in the Monitoring Management Plan (MMP). The SDV consists of a comparison of the source documentation and other relevant records to the eCRFs. This will require direct access to all original records for each subject.

It will be verified that documentation of the informed consent is on file for all subjects screened whether or not they were randomized into the study.

13.4 Completion of Electronic Case Report Forms

eCRFs must be completed for each subject enrolled in the trial, including screening failures. eCRFs should be completed as soon as possible after the subject visit. All eCRFs must be checked for consistency, accuracy, and completeness by the responsible Investigator, as well as, personally electronically signed and dated.

13.5 Data Management

The study Data Management Plan (DMP) will describe the methods used to collect, check and process clinical data, as well as the process for database locks. The DMP will be developed by the CRO and approved by Nicox. It will also list the roles and responsibilities of the various functions and personnel involved in the data management process.

The database lock [redacted].

13.6 Audits and Inspections

Authorized representatives of Nicox or the CRO, a regulatory authority, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of such audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the approved protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator must contact Nicox or CRO immediately if contacted by a regulatory agency about an inspection at their site.

The presence of the CRA at the site is mandatory in case of an inspection or audit (at least for the SDV audit and the debriefing with the Principal Investigator). Nevertheless, when justified, the CRA may be represented by another CRO representative involved in the study (e.g., lead CRA).

13.7 Access to Source Data

Nicox, authorized representatives of the CRO, or regulatory authority representatives will be allowed to have full and direct access to the various records relating to the trial (i.e., subject's data records) to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being reported.

13.8 Training of Staff

The Principal Investigator will maintain records of all individuals at their site involved in the study (medical, nursing, and other staff). The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the study staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved. The Principal Investigator must inform the CRA, in a timely manner, of any change in the study site staff.

13.9 Changes to the Protocol

Neither the Investigator nor the site staff may implement any changes to the protocol without approval by Nicox and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers). If a protocol amendment requires a change to a particular site's Informed Consent Form, then Nicox or the CRO and the site's IRB must be notified. Approvals of the revised Informed Consent Form by Nicox or the CRO, and the IRB are required before the revised form is used.

Nicox or the CRO will distribute amendments and new versions of the protocol to each Principal Investigator(s) and site study staff for review and any applicable training.

14. ADMINISTRATIVE, LEGAL, AND ETHICAL ASPECTS

14.1 Conduct of the Trial

The trial will be conducted according to the protocol, the ICH Consolidated Guideline for Good Clinical Practice (ICH GCP E6 (R2) - March 2018), and the applicable regulatory requirements.

14.2 Ethical Principles

The study has to be conducted in accordance with the principles of the Declaration of Helsinki (1964), as amended or clarified by the General Assembly of the World Medical Association (World Medical Association Declaration of Helsinki, last amended October 2013).

14.3 Health Authorities and Institutional Review Board (IRB)

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56).

The study protocol and subject informed consent form must be submitted to the appropriate properly constituted IRB. The approval from the IRB must refer to the exact protocol title and number, and identify all documents reviewed and their corresponding versions. A list of the IRB review board members as well as a statement of compliance with GCP and applicable laws and regulations should also be provided. Copies of all IRB correspondence with the Investigator should be given to the CRO.

The CRO is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun.

The Principal Investigator is also responsible for providing the IRB with safety reports of any unexpected SAEs from any clinical study conducted with the study medication, as dictated by the IRB requirements. These safety reports will be provided to the Principal Investigator by the CRO.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol. In addition, the IRB must approve all materials used to recruit subjects for the study. Either the Principal Investigator, or the CRO, must submit progress reports to the IRB according to the IRB requirements and local regulations and guidelines. The Principal Investigator must also provide the IRB with any reports of Serious Adverse Events from the study site, as dictated by the IRB requirements.

14.4 Subject Information and Consent

It is the responsibility of the Investigator to obtain written and signed informed consent prior to enrollment into the study (i.e., at the Screening Visit) and before any procedure related to the trial is performed.

The methods of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50 “Protection of Human Subjects”, the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements.

The Investigator or their designee must fully explain and adequately inform the subject of the purpose of the study prior to entering a subject into the clinical trial or performing any trial-specific procedures.

Once the subject fully agrees to participate in this study, written ICF must be documented by the subject's personally dated signature and the personally dated signature of the informing Investigator/designated person conducting the informed consent discussion. The subject will receive one copy and the original ICF will be filed in the subject study file on site.

The dates when the written informed consent was obtained for the subject and when the subject withdraws or exits the study, must be documented in the subject source documents so that it is known if the subject is currently participating in a clinical study.

In signing the ICF, a subject accepts direct access to their data by Nicox, the CRO, CRA, auditor, and Health Authority representatives.

14.5 Confidentiality Regarding Trial Subjects Data

In order to maintain subjects' privacy, all study materials will identify subjects in a fully anonymized manner. The Investigator will grant the company or its designated representatives, or regulatory authorities the right to access subject's original medical records for verification of the data gathered in the study. Subject's confidentiality will be maintained and will not be made publicly available unless mandated by applicable laws and regulations.

14.6 Archiving at the End of the Study

After the close-out visit at each site, the study is considered completed. A copy of the final completed CRFs will be stored in the Investigator's archives for up 2 years following the final approval of the last marketing authorization, together with all the other site study-specific documents (including Investigator's site file). Neither of these is ever transferred to the Sponsor.

All study-related materials must be stored in a secure manner and must remain available upon request from Nicox or any Health Authority.

14.7 Coordinating Investigator

The coordinating investigator [redacted]

15. PUBLICATION POLICY

The institutions, investigators, and all study personnel shall regard all study data as confidential until analyses and review of the analyses are performed by Nicox.

The institutions and investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of Nicox.

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APPENDIX 1: TIME AND EVENTS TABLE

	Screening Visit [a] (day -14 to -7)	Baseline/ Day 1 Visit	Day 4 Visit (± 1 day)	Day 8 Visit (± 1 day)	Day 11 Visit (± 1 day)	Day 15 Visit (- 1 day)	Day 29/ Exit Visit (± 2 days)
Informed Consent/HIPAA	X	-	-	-	-	-	-
Screening Number and Registration	X	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-
Medical/Ophthalmic History & Update	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Urine Pregnancy Test	X	-	-	-	-	X	-
Eye Dryness (VAS) [redacted]	X	X	-	X	X	X	X
Best Corrected Visual Acuity (ETDRS)	X	X	X	X	X	X	X
Eyelid Evaluation	X	-	-	-	-	-	-
Eyelid Evaluation [redacted]	-	X	X	X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X
[redacted]	X	X	-	X	X	X	X
Fluorescein Staining [redacted]	X	X	-	X	X	X	X
[redacted]	X	X	-	X	X	X	X
IOP	X	X	X	X	X	X	X
[redacted]	X	X	-	-	-	X	-
Eyelid Scrubs [c]	-	X	X	X	X	X	X
Study Medication Application [redacted]	-	X [d]	X	X	X	-	-
Dilated Ophthalmoscopy	X	-	-	-	-	-	X
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-
Randomization	-	X	-	-	-	-	-
Dispense Study Medication, Study-related Material, Diary and Instructions	-	X	-	-	-	-	-
Review of Subject Diary	-	-	X	X	X	X	-
Collection of Study Medication and Diary	-	-	-	-	-	X	-
Eyelid Scrub & Study Medication Application Training	-	X	-	-	-	-	-
Adverse Event Query	X	X	X	X	X	X	X
Study Exit	-	-	-	-	-	-	X

a) Screening Visit may be performed at any time of the day.
b) Subject-rated eyelid discomfort will be assessed prior to investigator-evaluated eyelid margin redness and eyelid debris
c) Daily eyelid scrubs will be performed prior to study medication application by the subject when self-administering study treatment. On applicable study visit days eyelid scrubs and study medication application will be performed at the site by the subject under the supervision of the study staff.
d) At the Baseline/Day 1 Visit, study medication is administered by the subject after site confirmation of eligibility and randomization. Subjects will be instructed on proper application technique.

APPENDIX 2: METHODS OF CLINICAL EVALUATION

For all assessments, sites should use the same instrument(s), method and examiner whenever possible throughout the study. All ophthalmic assessments will be performed bilaterally. The right eye will be assessed first, then the left eye.

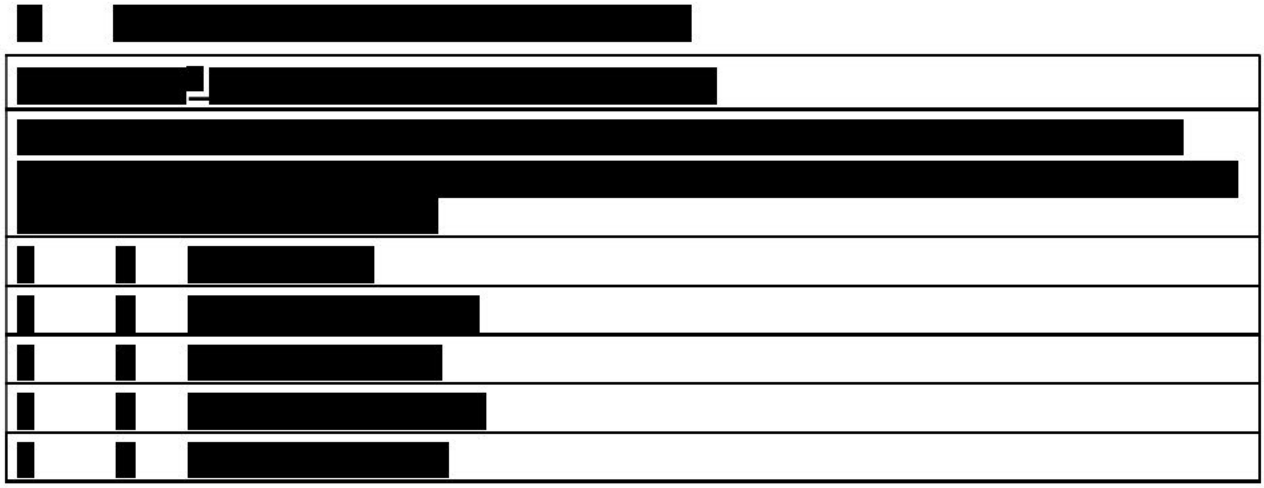
1. URINE PREGNANCY TEST

Urine pregnancy test is to be conducted on site by study staff per the instructions on the pregnancy kit.

2. EYE DRYNESS SCALE USING THE VISUAL ANALOGUE SCALE (VAS)

Subjects will be asked the following questions regarding ocular discomfort (unrelated to study drug instillation).

[redacted]



4. BEST CORRECTED VISUAL ACUITY (BCVA)

Procedure

LogMAR Visual Acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual Acuity should be evaluated prior to slit-lamp examination or contact with the eye (eg., tonometry). Visual acuity testing should be done with best (most recent) correction.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). 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 should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well illuminated.

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 the last line attempted where a letter was read correctly. 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 as well as 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.

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 during the entire study. The same correction should be used for a subject 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.

5. EYELID EVALUATION

The Eyelid Evaluations will be performed bilaterally (upper and lower eyelids) at each specified visit.

5.1 Subject-Evaluated Symptoms

[redacted] **Eyelid Discomfort Scale**		
[redacted]		
0	=	No eyelid discomfort
1	=	Mild discomfort [redacted]
2	=	Moderate discomfort [redacted]
3	=	Severe discomfort [redacted]
[redacted]		

5.2 Investigator-Evaluated Signs

[redacted] Eyelid Margin Redness Scale			
None	0	=	[redacted]
Mild	1	=	[redacted]
Moderate	2	=	[redacted]
Severe	3	=	[redacted]
[redacted]			

Ora Calibra® Eyelid Debris Scale			
None	0	=	[redacted]
Mild	1	=	[redacted]
Moderate	2	=	[redacted]
Severe	3	=	[redacted]
[redacted]			

6. SLIT LAMP EXAMINATION

The slit lamp examination will be performed prior to any contact assessments and instillation of any drops at each specified visit and at the discretion of the Investigator.

Each structure will be graded [redacted] The following structures will be examined at each visit:

- Eyelid (other than eyelid margin redness and eyelid debris)
- Conjunctiva [redacted]
- Cornea
- Lens
- Iris/Pupil
- Anterior Chamber

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9. CORNEAL [redacted] STAINING

9.1 Fluorescein Staining

If sodium fluorescein solution has not already been instilled [redacted], the examiner [redacted].

[redacted] Corneal and [redacted] Staining Scale for Grading of Fluorescein Staining			
[redacted]			
None	0	=	[redacted]
Trace	1	=	[redacted]
Mild	2		[redacted]

Moderate	3	=	[redacted]
Severe	4	=	[redacted]
[redacted].			

[redacted]

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

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

11. INTRAOCULAR PRESSURE (IOP)

Intraocular pressure will be measured by qualified study site personnel at each specified visit using a Goldmann applanation tonometer affixed to a slit lamp and in accordance with the site's standard practice. Two measurements will be obtained and the mean of the two readings will be calculated and recorded. If the first two measurements differ by more than 2 mmHg, a third measurement will be obtained and the median (middle) IOP will be recorded.

12. DILATED OPHTHALMOSCOPY

Dilated ophthalmoscopy will be performed at each specified visit.

The Investigator's preferred diagnostic dilating drop should be used and examination will be performed once the subject's eyes are deemed sufficiently dilated in the opinion of the Investigator. All structures will be graded [redacted] The cup-to-disc ratio will be recorded horizontally and vertically, and reported in 0.1 increments. The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve
- Cup-to-Disc

All findings should be recorded with appropriate medical terminology avoiding colloquialisms and abbreviations.

APPENDIX 3: GENERAL INSTRUCTIONS FOR COMPLETION OF SAE FORMS

1. As soon as possible, and at the latest within 24 hours of becoming aware of event, complete an initial SAE Form. The SAE Form must be completed with a black ink ball point pen, in English and with block capitals to facilitate the readability of the submitted document. Please ensure that all sections have been completed.
2. Evaluate the events of trial subjects and record on the case report form a diagnosis (when possible and appropriate) rather than each individual sign and symptom.
3. Terms such as death, hospitalization or a procedural name are not acceptable event terms.
    - Example: Subject was hospitalized for cholecystectomy due to cholecystitis. The event term would be "Cholecystitis" (not the procedure).
    - Example: "Death" is an outcome not an event term. The Investigator should report the primary cause of death as the SAE term.
4. All initial SAE reports must have the relationship to study medication documented.
5. All SAEs will be:
    - Followed to resolution (subject's health has returned to their baseline status or all variables have returned to normal) or
    - Followed until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event) or
    - The event is followed up to 30 days after last study medication application.
    - Some events do not end, such as metastasis; however, once these events are determined by the Principal Investigator to be stable or chronic, the PI may consider the event to be resolved or resolved with sequelae.
6. In case of death:
    - Specify the cause of death (do not use the term "death" and avoid using cardiac arrest or respiratory failure if possible. Instead, provide the diagnosis leading to cardiac arrest or respiratory failure.)
    - There should be only one SAE with an outcome of death for each subject.
    - For other adverse events that were ongoing at the time of death, enter outcome of these events as 'Ongoing.'
    - Please submit a copy of the Death Certificate and Autopsy Report (if applicable).
7. Review all source documents (examples - hospital discharge summary, hospital notes) as additional SAEs may be detected. If there are any questions as to whether you think an additional SAE may be present, please contact the Medical Monitor to discuss.
8. Protect the subject's identity. Redact all individually identifiable information (e.g., subject's name, medical record number, social security number and any parent or spouse

information such as names and addresses) in the header as well as in the body of the text on any supporting documents.

9. Follow-up SAE form completion instructions:
   - Complete and submit further Follow-up Reports for data collected until the SAE has resolved or a decision for no further follow up has been taken.
   - Complete a new SAE Form. At the top of the first page, tick the follow-up report or final report box and fax all pages even if changes were only made to one of the pages
   - Retain the submission confirmation.
10. In case of mistake on the original initial SAE Form submitted to the SAE contact person, correct it, date and sign it and submit it again. Retain the submission confirmation.
11. Downgrading/deletion of a previously reported SAE:

    If the Investigator determines a previously reported SAE doesn't meet serious criteria, a Follow-up SAE report should be completed. Document in the "Event Summary" section a brief explanation of why the Investigator determined the event to not be serious (*i.e.*, "it was determined that the subject was not hospitalized; therefore, this event does not meet serious criteria" or "the event was determined to be past medical history")
12. File original forms in the Case Report Form (CRF) of the subject.
13. Inform the IRB per IRB requirements and as required by local regulations.