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| **Protocol Title:** | A Phase 2, randomized, prospective, double-masked, vehicle-controlled study to assess the efficacy and safety of Nexagon® (NEXAGON) applied topically in subjects with corneal persistent epithelial defects (PED) resulting from severe ocular chemical and/or thermal injuries. |
| **Protocol Abbreviation:** | N**EX**AGON for the treatment of corneal **PED**s following S**E**VERE ocular chemical and/or thermal injuries (**EXPEDE**) |
| **Protocol Number:** | NEX-PED-005 |
| **Version:** | 6 |
| **Compound:** | Nexagon® (NEXAGON) |
| **Comparator:** | Nexagon® vehicle (Vehicle) |
| **Effective Date:** | 19April 2022 |
| **Sponsor:** | Amber Ophthalmics, Inc.<br>6020 Cornerstone Court West<br>Suite 100<br>San Diego, CA 92121<br>USA |

## STUDY DESCRIPTION

This is a Phase 2 randomized, prospective, double-masked, vehicle-controlled, multi-center study to evaluate the efficacy and safety of two topical ocular dose concentrations of NEXAGON as a treatment for non-healing corneal persistent epithelial defects (PEDs) resulting from severe chemical and/or thermal ocular injuries.

The primary efficacy endpoint for this study will be corneal epithelial recovery, defined as a cornea that re-epithelializes [redacted] and remains re-epithelialized for at [redacted] after initial re-epithelialization was first recorded.

[redacted]

Safety will be determined by the incidence of Treatment Emergent Adverse Events during the course of the study.

Potentially eligible subjects will be those who present with a clinically non-infected PED resulting from a severe chemical and/or thermal injury. Clinical signs of the ocular injury include de-epithelialization, conjunctival inflammation (hyperemia), limbal ischemia and corneal edema refractory to standard of care. Prior to enrollment, the PED must have been present for a minimum of 14 days, [redacted] and in the opinion of the Investigator, [redacted]

Eligibility of a subject will be confirmed if they meet all of the inclusion criteria and have no exclusion criteria.

On Day 1 of the Treatment Period, subjects will be randomly assigned [redacted] to receive either NEXAGON [redacted] or NEXAGON [redacted] or Vehicle 0% applied to their study eye in addition to continuing on the prescribed standard of care (SOC) regimen. SOC will remain unchanged for the duration of the study treatment, [redacted] IP will be re-applied [redacted]. If re-epithelialization has not occurred [redacted] subjects will receive another application of the masked investigational product. If re-epithelialization occurs [redacted] during the masked Treatment Period, subjects will enter a [redacted] Post-healing Follow-up Period to assess durability of the corneal epithelium. If, however, by [redacted] of the masked Treatment Period, re-epithelialization has still not occurred, all subjects irrespective of the investigational product assignment at randomization will be eligible to receive [redacted] If corneal re-epithelialization healing is still not achieved, these subjects will exit the study. If re-epithelization occurs, subjects will enter a [redacted] Post-healing Follow-up Period to assess durability of the corneal epithelium.

At the time of study enrollment, the size of the PED will be measured following staining of the cornea with fluorescein dye using a slit lamp biomicroscope [redacted] No ocular drops or ointments, prescribed as part of the standard of care regimen, will be permitted for [redacted] application of investigational product. Investigational product will be applied [redacted] the study eye. [redacted]

Study visits during the [redacted] Treatment Period will include assessment of re-epithelialization, measurement of the size of the PED, visual acuity, ocular symptoms, adverse events and use of concomitant medications.

At the time of re-epithelialization. [redacted], the subject will enter a Post-healing Follow-up Period where durability of the corneal epithelium will be assessed [redacted] after initial healing. The subject will then exit the study.

If, after initial epithelialization, the epithelium breaks down within the [redacted] Post-healing Follow-up Period the subject will exit and receive [redacted] salvage dose applications of NEXAGON [redacted] within the open-label section of the study. If re-epithelialization occurs by [redacted], a final assessment of the epithelium will be performed [redacted] later to determine durability.

## REVISION CHRONOLOGY

| Version Number | Version Date | Summary of Revisions |
|---|---|---|
| Version 1 | [redacted] | [redacted] |
| Version 2 | [redacted] | [redacted] |
| Version 3 | [redacted] | [redacted] |

| Version Number | Version Date | Summary of Revisions |
|---|---|---|
| | | [redacted] |

| Version Number | Version Date | Summary of Revisions |
|---|---|---|
| | | [redacted] |
| Version 4 | [redacted] | [redacted] |
| Version 5 | [redacted] | [redacted] |

| Version Number | Version Date | Summary of Revisions |
|---|---|---|
| Version 6 | [redacted] | [redacted] |

## INVESTIGATOR SIGNATURE PAGE

I confirm agreement to maintain the protocol in confidence and to conduct the study in compliance with the protocol, good clinical practice and all applicable regulations.

| _____ | _____ | _____ |
|---|---|---|
| Investigator Printed Name | Signature | Date (dd/mmm/yyyy) |

## SPONSOR SIGNATORY/SIGNATORIES

[redacted]

19Apr2022

Date (dd/mmm/yyyy)

## SPONSOR INFORMATION

## AMBER OPHTHALMICS, INC. ("AMBER")

**Amber Office:** [redacted]

**Medical Monitor:** [redacted]

**Sponsor Contacts:** [redacted]

**Regulatory Agency Identifying Number(s):** [redacted]

## LIST OF ABBREVIATIONS

| | |
|---|---|
| < | Less than |
| > | Greater than |
| ≤ | Less or equal to |
| ≥ | Greater or equal to |
| % | Percent or percentage |
| AE | Adverse event |
| ALT | Alanine transaminase |
| Amber | Amber Ophthalmics, Inc. |
| AMT | Amniotic membrane transplant |
| API | Active pharmaceutical ingredient |
| AST | Aspartate aminotransferase |
| ATP | Adenosine triphosphate |
| [redacted] | [redacted] |
| BCVA | Best Corrected Visual Acuity |
| ºC | Degrees Celsius |
| CF | Counting Fingers |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CODA001 | Active pharmaceutical ingredient |
| CRA | Clinical Research Associate |
| CRF | Case report form |
| CV | *Curriculum vitae* |
| ECG | Electrocardiogram |
| *e.g.* | *Latin,* exempli gratia (for example) |
| *et al.* | *Latin*, et alii (and others) |
| *etc.* | *Latin,* et cetera (and other similar things) |
| ETDRS | Early treatment diabetic retinopathy study |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FUP | Follow-up |
| GCP | Good clinical practice |
| GLP | Good laboratory practice |
| $HbA1_c$ | Hemoglobin $A1_c$ |
| HM | Hand movements |
| HSV | Herpes simplex virus |
| HZV | Herpes zoster virus |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | Identification |

| | |
|---|---|
| *i.e.* | *Latin*, id est (that is) |
| IEC | Independent ethics committee |
| IP | Investigational product |
| IOP | Intraocular pressure |
| IRB | Institutional review board |
| kg | Kilogram(s) |
| LAR | Legally authorized representative |
| LOCF | Last observation carried forward |
| µg | Microgram(s) |
| µL | Microliter(s) |
| mg | Milligram(s) |
| mL | Milliliter(s) |
| mm | Millimeter(s) |
| mmHg | Millimeter of mercury |
| MP | Megapixel |
| mRNA | Messenger ribonucleic acid |
| NEXAGON (Nexagon®) | Formulation with active pharmaceutical ingredient |
| NOEL | On observed effect level |
| NPL | No perception of light |
| P or p | Probability |
| PED | Corneal persistent epithelial defects |
| pH | Potential of hydrogen |
| PL | Perception of light |
| PP | Per protocol population |
| PRK | Photorefractive keratectomy |
| PT | Preferred term |
| ® | Registered trademark |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SMO | Site management organization |
| SOC | System organ class |
| TEAE | Treatment emergent adverse event |
| UCVA | Uncorrected visual acuity |
| U.S./USA | United States/United States of America |
| VA | Visual acuity |
| Vehicle | Nexagon® vehicle |
| WMA | World Medical Association |

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## PROTOCOL SYNOPSIS

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|---|---|
| **Title** | A Phase 2, randomized, prospective, double-masked, vehicle-controlled study to assess the efficacy and safety of Nexagon® (NEXAGON) applied topically in subjects with corneal persistent epithelial defects (PED) resulting from severe ocular chemical and/or thermal injuries. |
| **Study Population** | This protocol will enroll up to a **maximum of [redacted] subjects.** A total of [redacted] subjects are required to complete this study.<br><br>All eligible subjects will present with a non-infected, corneal PED as a result of a chemical and/or thermal ocular injury which is refractory to current standard of care for at least 14 days. |
| **Study Objective** | The objective of this protocol is to assess the efficacy and safety of two topical ocular dose concentrations of NEXAGON as treatment of non-healing corneal PEDs resulting from severe chemical and/or thermal ocular injuries. |
| **Endpoints** | Primary Endpoint:<br>• Corneal epithelial recovery, defined as a cornea that re-epithelializes by [redacted] of treatment and remains re-epithelialized for at least [redacted] after initial re-epithelialization was first recorded, as assessed by the Investigator.<br>Secondary Endpoints:<br>[redacted]<br>Exploratory Endpoints:<br>[redacted]<br>Safety:<br>• Incidence of Treatment Emergent Adverse Events. |

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| **Study Periods/Duration** | The study will comprise a [redacted] Treatment Period and a Post-healing Follow-up Period of [redacted] both of which are double-masked.<br><br>Once determined to be eligible, subjects will be randomized to receive either NEXAGON [redacted] or NEXAGON [redacted] or Vehicle in a [redacted] ratio respectively. Investigational product will be applied [redacted] during the Treatment Period:<br><br>▪ [redacted]<br>▪ [redacted]<br>▪ [redacted]<br><br>However, if by [redacted] of the Treatment Period the cornea has not fully re-epithelialized, irrespective of the investigational product assignment at randomization, subjects will enter the open-label section of the study and will receive [redacted] applications of NEXAGON [redacted] NEXAGON [redacted] will be applied [redacted] Subjects receiving salvage therapy will be followed from the first salvage dose application to determine if re-epithelialization occurs [redacted].<br><br>For each subject, the [redacted] masked Treatment Period will end when *EITHER,* corneal re-epithelialization is [redacted] recorded following up to a maximum of [redacted] applications of investigational product *OR* subjects enter the open-label section of the study as a result of an unhealed PED [redacted].<br><br>Those subjects who achieve re-epithelialization will immediately begin the [redacted] Post-Healing Follow-up Period. No further investigational product will be applied. The aim of the post epithelialization follow-up period is to assess the durability of the epithelium.<br><br>For those subjects that achieve re-epithelialization but epithelialization is NOT sustained during the [redacted] Post-healing Follow-up Period, the subject will become eligible to receive the salvage dose(s) of NEXAGON [redacted] and enter the open-label section of the study [redacted] If re-epithelialization is not achieved [redacted] a second dose of NEXAGON [redacted] will be applied. If re-epithelialization occurs [redacted], a final assessment of the epithelium durability will be performed [redacted].<br><br>Subjects will also exit the study if re-epithelialization is not achieved [redacted] in the open-label section of the study.<br><br>The MAXIMUM duration for study participation for a subject is [redacted] |

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| | ***Refer to Table 1: Schedule of Assessments for details of the visit schedule and the procedures to be conducted at each study visit.*** |
| **Investigational Product Administration for Randomized Subjects** | Each investigational product dose application [redacted]<br><br>No topical ocular standard of care treatment will be permitted [redacted] before or [redacted] following investigational product administration. [redacted]<br><br>Three treatment arms will be evaluated in this study. Randomization will be in a [redacted] ratio:<br>• GROUP A – NEXAGON [redacted]<br>• GROUP B – NEXAGON [redacted]<br>• GROUP C – Vehicle<br><br>There will be a single application of investigational product [redacted]. A potential additional application of investigational product will be scheduled [redacted] if re-epithelialization has not occurred.<br><br>If re-epithelialization of the study eye has still not occurred at the end of the [redacted] masked Treatment Period, or following initial re-epithelialization durability is not maintained, subjects will receive [redacted] salvage dose applications of - NEXAGON [redacted] in the open-label section of the study |
| **Study Description** | Potentially eligible subjects will be those who present with a clinically non-infected PED as a result of a severe chemical and/or thermal injury refractory to standard of care. Clinical signs of the ocular injury include de-epithelialization, conjunctival inflammation (hyperemia), limbal ischemia and corneal edema.<br><br>Before the entry of a subject can be considered, the PED must have been present for at least 14 days, [redacted]<br><br>Subject consent to participate in the study must be obtained by the Principal Investigator or suitably qualified designee before any protocol-specific procedures are undertaken. Eligibility assessments and baseline evaluations will be performe [redacted] |

[redacted]

The first investigational product application will occur following randomization [redacted] The eye will then be covered with a double eye pad and taped shut for approximately [redacted].

[redacted]

**Each subject will attend twice-weekly assessment visits until corneal re-epithelialization occurs.**

**If re-epithelialization of the defect has NOT occurred by [redacted] of the masked Treatment Period**, another single application of masked investigational product will be administered.

**If corneal re-epithelialization has NOT occurred by [redacted] of the masked Treatment Period,** subjects will receive [redacted] salvage dose applications of NEXAGON [redacted] in the open-label section of the study. [redacted] If re-epithelialization has not occurred [redacted] the subject will exit the study.

**Once re-epithelialization has occurred,** [redacted] **,** the subject will enter the Post-healing Follow-up Period [redacted] Subjects will be assessed [redacted] following initial re-epithelialization to confirm durability of the epithelium. The subject will then exit the study having completed all visits.

**If, after initial epithelialization, the epithelium breaks down within the [redacted] Post-healing Follow-up Period**, the subject will receive [redacted] salvage dose applications of NEXAGON [redacted], in the open-label section of the study.

**If a re-epithelialized cornea develops** [redacted], these subjects will also be followed for [redacted] to assess durability of healing [redacted].

Refer to Figure 2: Study Flow Diagram [redacted]

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| | At each study visit following randomization until the end of the Treatment Period, the subject will undergo assessments as detailed in Table 1: Schedule of Assessments. Assessments will include [redacted] The occurrence of any Treatment Emergent Adverse Events will also be assessed at each study visit, and up to [redacted] following the final application of investigational product. |
| **Standard of Care during the Treatment Period and the Open-label section of the study** | During the Treatment Period and the open-label section of the study, EXCEPT for [redacted] before and the [redacted] period after investigational product administration, the subjects will continue to receive the standard of care regimen prescribed to them by the Investigator at the study site.<br>**Details of the medications administered, doses and dosing regimens** must be recorded in the source documentation and case report form.<br>[redacted]<br>Systemic standard of care will not be defined by the protocol but by the Investigator's or study site routine practice. However, systemic medications and regimen for the treatment of the PED should remain unchanged for the duration of the study, until re-epithelialization or study exit.<br>*NOTE: Use of topical anesthetic drops will ONLY be permitted for ophthalmic assessments conducted at each study visit.* |
| **Inclusion/Exclusion Criteria** | **INCLUSION CRITERIA**<br>**A subject will be eligible for inclusion in this study only if ALL of the following criteria apply:**<br>1. Male and female of any age.<br>2. Clinically non-infected, corneal persistent epithelial defect (PED) as a result of a severe chemical and/or thermal ocular injury in one or both eyes.<br>3. [redacted]<br>4. [redacted]<br>5. Providing written informed consent and ability to comply with the visit and dosing schedule. |

NOTES:

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

**EXCLUSION CRITERIA**

**A subject will not be eligible for inclusion in this study if ANY of the following exclusion criteria apply:**

1. [redacted]
2. Have active clinically significant ocular infection.
3. Subjects with corneal perforation or impending corneal perforation.
4. Subjects with any other past or present ophthalmic disease or medical condition that, in the Investigator's opinion, may affect the safety of the subject or the outcome of the study.
5. Treatment with systemic corticosteroids [redacted]
6. Subjects with severe lid abnormalities as a result of the injury contributory to the persistence of the epithelial defect such as inability to close the lids.
7. Subjects with a history of severe ocular conditions contributory to the persistence of an epithelial defect prior to the injury.
8. Female subjects of childbearing potential who are pregnant, nursing, planning a pregnancy or not using an adequate and medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is a) post-menopausal (defined as at least 12 months of amenorrhea), b) surgically sterilized and at least 3 months post-surgical, or c) using a hormonal contraceptive, intra-

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| | uterine device, diaphragm with spermicide, or condom with spermicide for the duration of the study.<br>9. Subjects who have participated in an interventional clinical trial within 30 days prior to Day 1. |

**Figure 1:** [redacted]

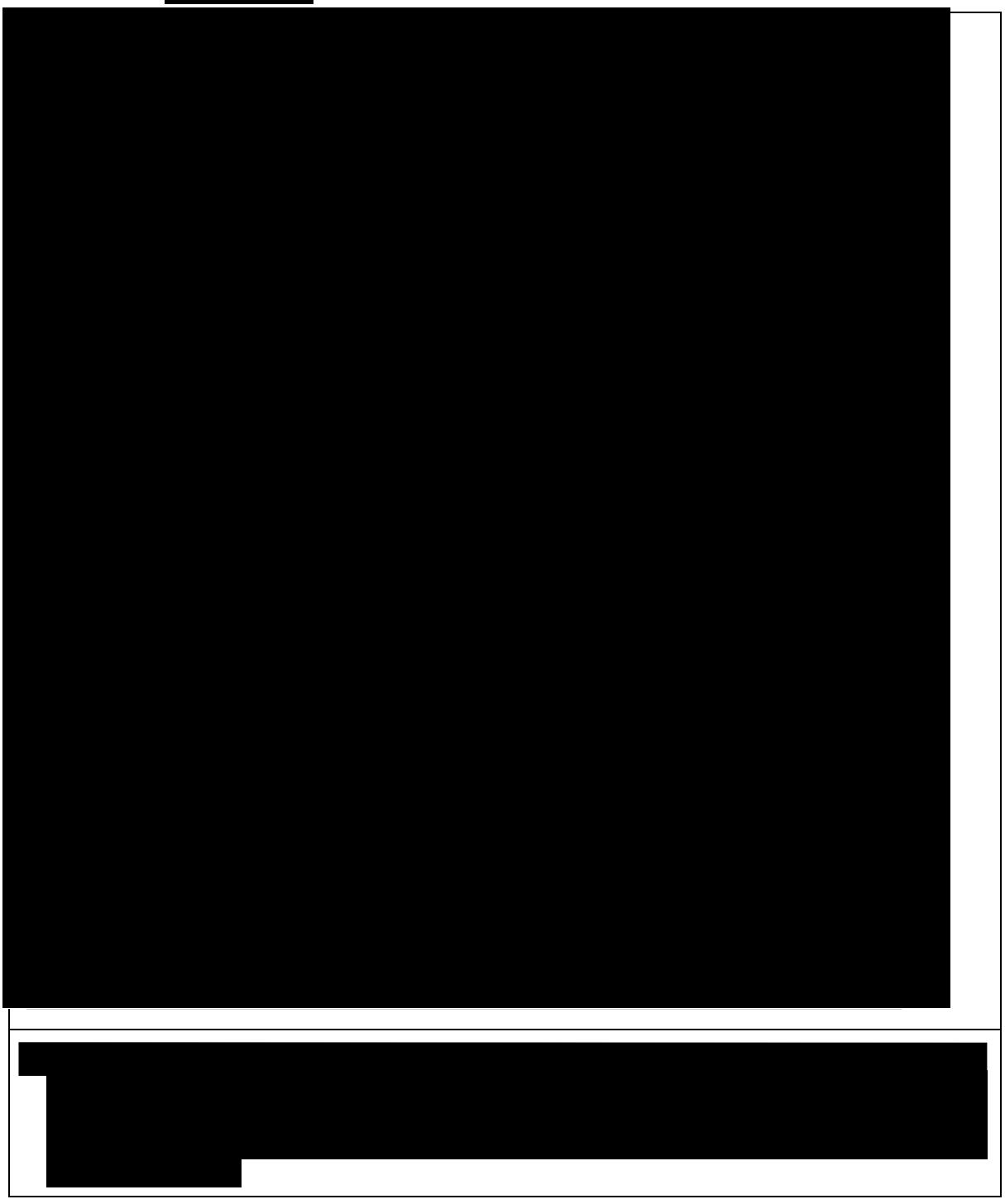


**TABLE 1:** [redacted]

[redacted]

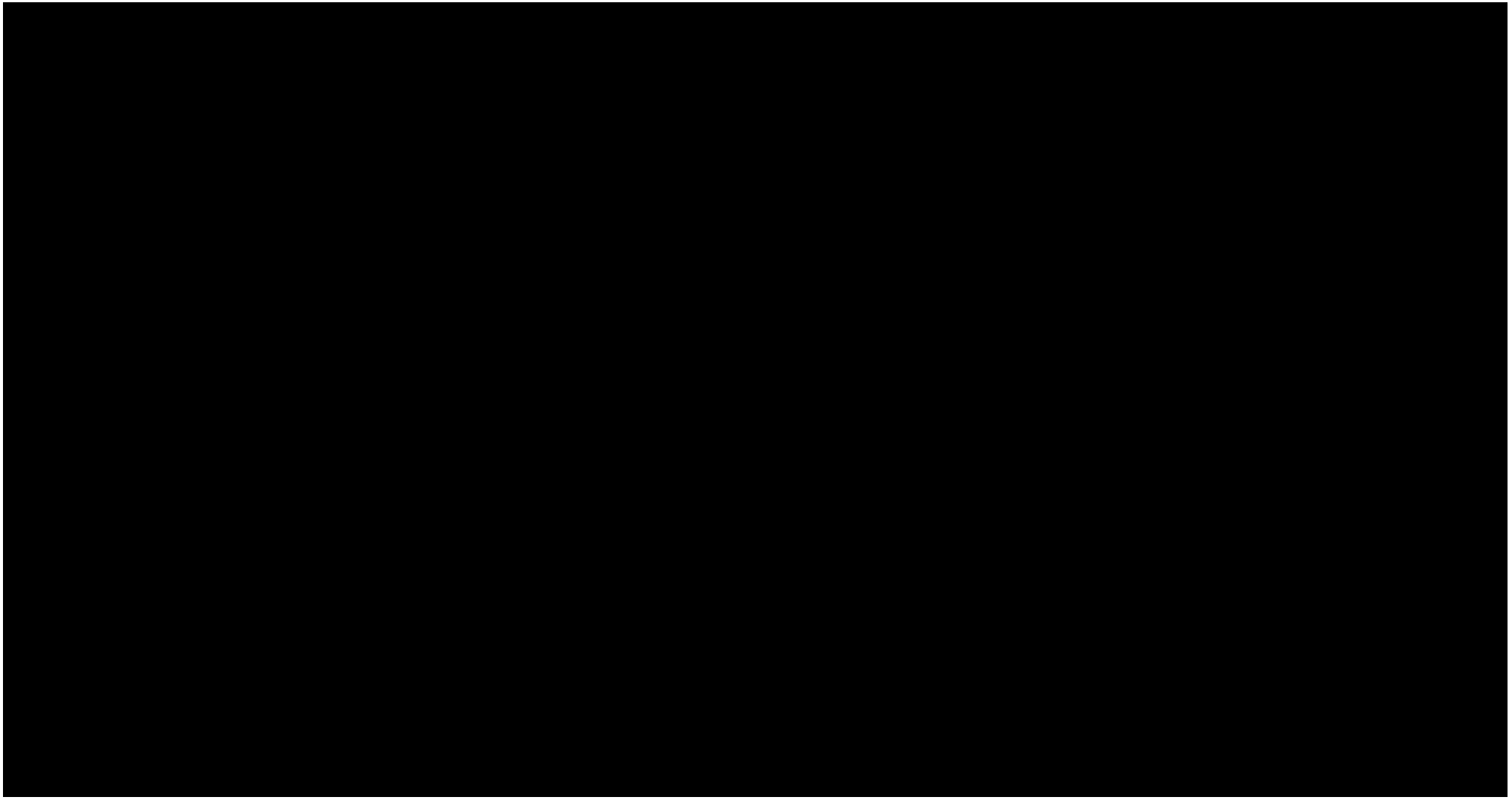


**Figure 2:** [redacted]

# 1. INTRODUCTION

## 1.1. Background

Chemical and thermal injuries to the eye constitute a medical emergency (Spector and Fernandez, 2008) and can result in significant damage to the ocular surface and the anterior segment. Permanent unilateral or bilateral visual impairment may result (Spector and Fernandez, 2008).

An intact corneal epithelium is crucial for maintaining the integrity and functioning of the eye. Damage to the ocular surface results in impaired vision, pain and discomfort and leaves the eye susceptible to infection. After significant injuries, the full restoration of the cornea may never occur despite current standard of care (Farjo, 2004). In these cases of severe injury, failure of the epithelium to heal may result in blindness or loss of the eye. A key factor inhibiting the healing response and exacerbating tissue damage is excessive inflammation as seen with severe chemical and thermal injuries to the eye. The mainstay of treatment for a damaged corneal epithelium is to optimize the health of and protect the denuded cornea from further trauma in an effort to promote epithelial healing. However, not all patients will respond to standard treatment regimens leading to a defect in the corneal epithelium that may not heal and persists (Vajpayee *et al*., 2003).

These ocular wounds known as persistent corneal epithelial defects (PED) can be defined as a loss of the integrity of the corneal surface, caused by injury or disease, which does not heal within the normal timeframe, but persists for weeks or even months (McCulley *et al*., 1993). Subjects whose defect fails to heal with standard treatment can experience severe pain, foreign body sensation, tearing, blepharospasm, decreased visual acuity and photophobia (Oskouee *et al*., 2007). A novel therapeutic agent designed to reduce the cycle of inflammation, regenerate the microvasculature and blood flow, and promote epithelial healing could benefit those patient's refractory to standard of care.

Current treatments for PEDs that result from chemical and thermal injuries include corticosteroids, collagenase inhibitors, ascorbate, epidermal growth factors, autologous serum, amniotic membranes, tear supplements, therapeutic contact lenses and tarsorrhaphy. However, there is no treatment that can consistently improve outcomes in PED and relieve the associated severe disability experienced (Oskouee *et al*., 2007; Saw *et al*.,2007; Gordon *et al*., 1995; Williams *et al*., 1999).

## 1.2. Nexagon®

Nexagon® (NEXAGON) is a topical oligonucleotide [redacted] which is a selective inhibitor of connexin43 (Cx43) overexpression. NEXAGON is being developed for the treatment of chemical or thermal injury to the cornea resulting in a PED which is non-responsive to standard of care.

Overexpression of Cx43 leads to the assembly and recycling of the inflammasome pathway of inflammation resulting in ischemia and a non-responsive PED due to lack of microvascular blood supply at the limbus. NEXAGON has been shown to promote epithelial regeneration by breaking the cycle of inflammation, re-establishing microvasculature and blood flow, thereby promoting regeneration of the epithelium.

The active pharmaceutical ingredient (API) of NEXAGON is CODA001, which is an unmodified [redacted] oligonucleotide molecule. [redacted]

[redacted]

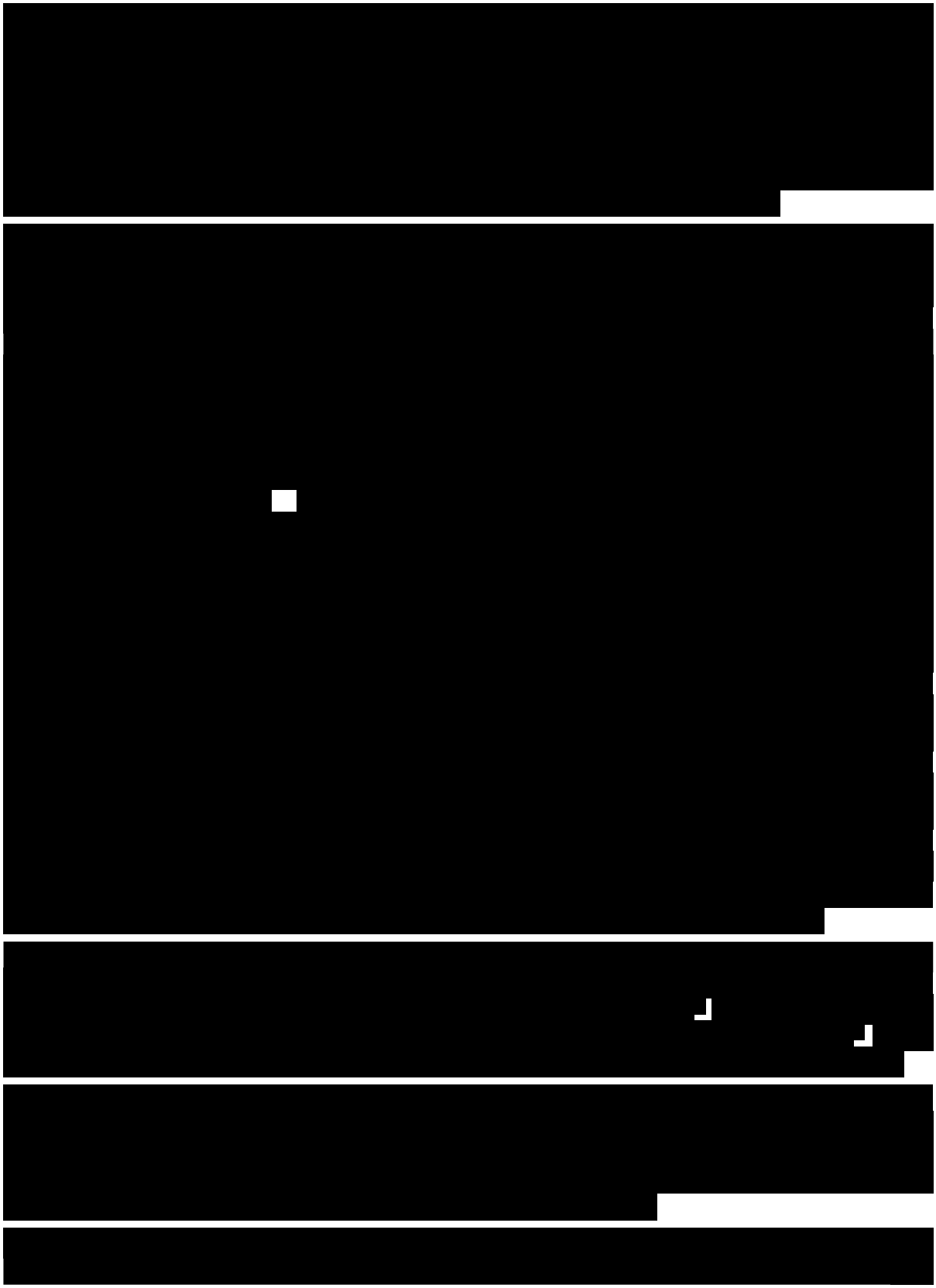
When applied directly to a wound by way of the NEXAGON formulation, CODA001 functions by hybridizing to connexin43 mRNA to temporarily inhibit local expression of connexin43 which results in temporary inhibition of hemichannel formation. The transient down-regulation of connexin43 results in a break of the inflammasome cycle and inflammatory cytokine levels which have been shown to inhibit wound healing (Kim *et al*., 2016; McCarty and Percival, 2013; Singer and Clark, 1999). Breaking the inflammasome cycle enables restoration of vascular integrity and tissue perfusion, and with respect to the ocular surface, it will restore limbal perfusion essential for corneal healing (Ormonde *et al*., 2012).

Down-regulation of connexin43 expression by CODA001 has been shown to promote healing in a number of preclinical *in vivo* animal and *ex vivo* tissue models, including skin lesions, and burns (Qiu *et al*., 2003; Coutinho *et al*., 2003; Grupcheva *et al*., 2012).

[redacted]

In the clinical setting, NEXAGON was shown to reduce inflammation and restore limbal perfusion to promote re-epithelialization in a number of patients treated in a compassionate use protocol following severe ocular chemical and/or thermal injuries resulted in PEDS refractory to standard therapies (Ormonde *et al, 2012)*.

### 1.2.1. Toxicology



[redacted]

All of these studies were conducted with small to very large multiples of clinical doses (with respect to the CODA001 dose level), and no toxicity was observed in any of the studies based on extensive evaluations of potential local and systemic effects.

### 1.2.2. Effects in Humans – Clinical Summary

The safety, tolerability and clinical effects of topical administration of NEXAGON have been investigated in four Phase 1 studies (one ocular and three dermal) and three dermal Phase 2 studies in venous leg ulcer and diabetic foot ulcer patients.

[redacted]

Human clinical experience with NEXAGON to date has indicated that NEXAGON has an excellent safety profile and is well tolerated. The only adverse events reported as being possibly related to NEXAGON were transient sensations of stinging/tingling/burning when administered to chronic venous ulcers (3 patients in total). No other possibly related or related adverse events or serious adverse events have been reported to date in any of the clinical studies and the 12 compassionate use patients.

Details of the ocular clinical studies and the isolated compassionate use for ocular applications are described in more detail in the latest edition of the Investigator's Brochure for NEXAGON® – Ocular Administration.

## 1.3. Study Rationale

There are a range of primary ocular surface disorders that can cause a defect of the corneal epithelium such as chemical injuries, thermal injuries, neurotrophic keratitis, keratoconjunctivitis sicca, cicatricial pemphigoid, Stevens-Johnson syndrome, or toxic epidermal necrolysis (Letko *et al*., 2001).

The purpose of this study is to investigate the effect of NEXAGON in treating wounds to the eye that have been caused by severe chemical and/or thermal injuries and which have remained unhealed [redacted] despite conventional medical and surgical standard of care treatment over that period.

NEXAGON, which is a topical gel [redacted], has [redacted]

As detailed in Section 1.2.2, Effect in Humans – Clinical Summary, encouraging clinical results have been shown in eight patients treated with NEXAGON on a compassionate use basis. Each patient had a PED as a result of chemical and/or thermal injuries and re-epithelialization of the cornea could not be achieved by standard of care alone. Details of all eight patients are provided in the latest edition of the Investigator's Brochure for NEXAGON - Ocular Administration [redacted]

The rationale for this current study is to determine, under a formal clinical protocol, whether NEXAGON is an effective treatment modality for PEDs that have developed as a result of severe chemical and/or thermal injuries, and which are non-responsive [redacted] Two dose concentrations of NEXAGON will be assessed against a Vehicle control.

## 1.4. Dose Concentration, Administration and Regimen Rationale

NEXAGON is formulated with two components, namely the active pharmaceutical ingredient (API), called CODA001 which is an unmodified [redacted] oligonucleotide [redacted]

NEXAGON [redacted] have been selected as the two dose concentrations to be used in this study. The comparator will be the Vehicle [redacted].

The primary endpoint will be corneal epithelial recovery, [redacted]

Previous dosing experiences of NEXAGON in ocular indications are as follows:

- **Study NEX-OCU-001:** A Phase 1, dose-rising safety study in 26 participants which assessed the safety of [redacted] of [redacted] of NEXAGON applied to the de-epithelialized eye following photo-refractive keratectomy. There were no side effects or dose-limiting toxicities attributable to any dose of NEXAGON in any of these subjects in this study. Therefore, all four dose concentrations were safe and tolerated when applied to a wounded human eye.
- **Study NTX-OCI-001:** A Phase 2 randomized, prospective, double-masked, vehicle-controlled study to evaluate the safety and efficacy of topical NEXAGON in subjects with ocular surface chemical burns. Subjects were randomized to either NEXAGON ([redacted]

[redacted] the equivalent volume of NEXAGON Vehicle. Investigational product was given on [redacted] in addition to the subjects receiving standard of care. Clinical doses of [redacted] was chosen largely based on the previous Phase 1 study and the anticipated effect of standard of care on NEXAGON application. No overt toxicity was seen in NEX-OCU-001 [redacted] or in the animal toxicology studies up to 32 mg/mL (3.2%) per eye. The study was closed due to slow enrollment after a total of 34 of 66 subjects were recruited, analysis of the data indicated that further investigation of the effects of NEXAGON in patients with severe ocular burns that are more difficult to heal was warranted in a subsequent trial.

- **Ocular Compassionate Use Cases:** Eight patients with a PED resulting from chemical or thermal injuries have been treated with NEXAGON on a compassionate use basis as re-epithelialization of the cornea could not be achieved by standard of care. The dose concentrations used in the compassionate use settings have included [redacted] and whilst some subjects had [redacted], others required [redacted] applications to achieve re-epithelialization. Total doses administered ranged from [redacted] to 8.2 mg (refer to the latest edition of the Investigator's Brochure for Nexagon® – Ocular Administration).

  For the first 6 compassionate use cases, NEXAGON was applied by being extruded from a syringe [redacted]. However, following Protocol NTX-OCI-001, the two most recent compassionate use patients received NEXAGON on [redacted] Re-epithelization was achieved in both these later subjects, although the most recent case also underwent bilateral AMT and further applications of NEXAGON to achieve healing.

- **Toxicology:** [redacted]

### 1.4.1. Dose Concentration Selection

Whilst prior ocular use in the compassionate use setting has demonstrated positive activity with dose concentrations [redacted] higher dose concentrations have also yielded encouraging results, especially in subjects with very severe ocular injuries. Due to the nature of these severe ocular injuries, it is expected that the increased inflammation and increased tearing in the eye will give a combined dilution effect on the applied topical drug.

[redacted]

The lower dose concentration of NEXAGON [redacted] provides continuity [redacted] used to treat 8 subjects under a compassionate use situation. Efficacy by way of re-epithelialization and preservation of the eyes, was demonstrated in this series of subjects after the PEDs were deemed refractory to standard of care. However, until now the dose concentration of

[redacted] has yet to be evaluated formally in a randomized, double-masked, controlled clinical trial setting.

Similarly, a higher dose concentration of NEXAGON [redacted] has also been selected for this study. This is because the severity of ocular injuries to be included in the study are associated with increased inflammation and increased tearing. [redacted] This dose is substantially lower than the dosing administered in toxicology study GLP-2017-0024, where multiple repeat applications of NEXAGON [redacted] were applied over [redacted] to mechanically wounded and non-wounded rabbit eyes. Study GLP-2017-0024 did not show any signs of toxicity, nor impede corneal re-epithelialization between wounding days.

### 1.4.2. Dose Administration and Regimen

A single dose administration of investigational product – either NEXAGON [redacted] or Vehicle – [redacted]

The dosing schedule for this study [redacted]

After randomization, investigational product will be administered [redacted]

For Protocol NEX-PED-005, the lowest dose concentration of NEXAGON [redacted] will equate to a total daily dose of [redacted] per application. This dose lies within the therapeutic window used for previous compassionate use patients and overlaps previous clinical experience. [redacted]

The compassionate use series of patients indicated that [redacted] may sometimes be required to attain re-epithelialization in the most severe or resistant cases. Therefore, if re-epithelialization has not occurred by [redacted] another investigational product application will be permitted. This dosing schedule is based on compassionate use experience and with the expectation that initial healing will likely begin immediately following the [redacted] doses. [redacted]

However, if by [redacted] corneal re-epithelialization has still not occurred, those subjects will receive [redacted] salvage dose applications of NEXAGON [redacted], irrespective of the investigational product assignment at randomization. The rationale for receiving [redacted] is

to enable all unhealed subjects enrolled into the study - particularly those randomized to Vehicle - the opportunity of receiving application(s) of investigational product at the highest dose concentration of NEXAGON available.

# 2. STUDY OBJECTIVES

The objective of this study is to assess the efficacy and safety of two topical ocular dose concentrations of NEXAGON as a treatment for non-healing corneal PEDs resulting from severe chemical and/or thermal ocular injuries.

# 3. STUDY ENDPOINTS

**Primary Endpoint**

- Corneal epithelial recovery, defined as a cornea that re-epithelializes by [redacted] of treatment and remains re-epithelialized for at [redacted] after initial re-epithelialization was first recorded, as assessed by the Investigator.

**Secondary Endpoints**

[redacted]

**Exploratory Endpoints**

[redacted]

**Safety**

- Incidence of Treatment Emergent Adverse Events.

# 4. INVESTIGATIONAL PLAN

## 4.1. Study Description

The purpose of this Phase 2 protocol is to evaluate the efficacy and safety of two topical ocular dose concentrations of NEXAGON in subjects with corneal PEDs arising from severe chemical and/or thermal injuries which are non-responsive to current standard of care.

Enrollment for this study will continue until [redacted] complete the study. Up to a maximum [redacted] in total will be randomized. The study is double-masked, and neither the Investigator, subject, nor Sponsor/CRO personnel involved in the day to day protocol activities will know which treatment group has been allocated. Subjects will be randomized to either Group A (NEXAGON [redacted]), Group B (NEXAGON [redacted]) or Group C (Vehicle).

Potentially eligible subjects will be those who present with a clinically non-infected persistent epithelial defect as a result of a severe chemical and/or thermal injury refractory to standard of care. Clinical signs of the ocular injury include de-epithelialization, conjunctival inflammation (hyperemia), limbal ischemia and corneal edema.

Before entry of a subject into this protocol can be considered, the PED must have been present for a minimum of 14 days, [redacted]

As detailed in the study entry criteria, for subjects presenting with bilateral ocular surface damage, only one eye will be eligible to be the 'study eye' [redacted]

*If the Investigator has any doubts about the eligibility of a subject, he/she will be advised to contact the study Sponsor/Medical Monitor to discuss the case further to determine whether the subject is eligible to participate in this protocol.*

All subjects who are considered for study inclusion will first have the study explained to them in full. If they are willing to participate, written informed consent will be obtained before any study-related procedures are performed. ONLY subjects that meet all of the inclusion criteria and have no exclusion criteria will be eligible for randomization to double-masked investigational product.

[redacted] No topical ocular drops or ointments are permitted within [redacted] prior to investigational product application or [redacted] after.

**The study will comprise of 2 periods**:

- [redacted] **masked Treatment Period**, where investigational product will be applied [redacted]. Each subject will attend [redacted] assessment visits until corneal re-epithelialization occurs. If by [redacted] re-epithelization has not occurred, the subject will enter the open-label section of the study and receive [redacted] salvage dose applications of NEXAGON [redacted]
- **Post-healing Follow-up Period**, which will commence as soon as re-epithelization occurs in the Treatment Period in order to assess durability of the healed cornea [redacted] later; the masking will remain during this period.

For all subjects, the first investigational product application will occur following randomization on [redacted]

Refer to Section 7 and the Pharmacy Manual for instructions on investigational product administration.

During the Treatment Period, masked investigational product will initially be administered [redacted]

If re-epithelialization of the defect has NOT occurred by [redacted] another single application of masked investigational product will be administered.

If re-epithelialization occurs [redacted] during the masked Treatment Period, subjects will enter a [redacted] Follow-up Period to assess durability of the corneal epithelium.

However, if by [redacted] of the masked Treatment Period, the cornea has still not fully re-epithelialized, then subjects will receive a salvage treatment dose of NEXAGON [redacted] If re-epithelialization has not been achieved after [redacted] a second salvage dose of NEXAGON [redacted] Final assessment of healing for these subjects will be conducted on [redacted]

If re-epithelialization has not occurred by [redacted] the subject will exit the study.

Once re-epithelialization has occurred, [redacted], the subject will enter the Post-healing Follow-up Period and [redacted]. Subjects will be assessed again [redacted] following initial re-epithelialization to confirm durability of the epithelium. The subject will then exit the study having completed all visits.

If the healed epithelium is not sustained within the Post-healing Follow-up Period, the subject will exit and receive the salvage dose(s) as part of the open-label section of the study. If a re-epithelialized cornea develops following the salvage dose application(s), these subjects will also be followed for [redacted] to assess durability of healing.

[redacted]

At each study visit, following randomization until the end of the study, the subject will undergo assessments as detailed in **Table 1 (Schedule of Assessments).** Assessments will be performed by a designee at the study site who is masked to the allocated investigational product [redacted] The occurrence of any Treatment Emergent Adverse Events will also be assessed at each study visit, and up to [redacted] following the final application of investigational product.

**Please refer to Table 1 (Schedule of Assessments) and to Section 6 for full details of study assessments and procedures required at each visit. Figure 2 (Study Flow Diagram) shows the schedule of visits and dosing days.**

### 4.1.1. Study Visit Windows

Subject's visit dates can be booked within the windows detailed in Table 1: Schedule of Assessments. Ensure that when determining the visit dates that these are done with reference to the Day 1 visit date of the Treatment Period and not the subject's previous visit. Visits that are not able to be completed within the windows specified in this protocol must be recorded as protocol deviations.

Note: Day 1 corresponds to the day of randomization, Day 0 is not utilized in this study design.

# 5. STUDY POPULATION

## 5.1. Number of Subjects and Centers

A total of [redacted] are required to complete this study. To allow for discontinuations, up to a maximum [redacted] with PED resulting from a severe chemical and/or thermal injury will be randomized. The study will be conducted at [redacted]

## 5.2. Inclusion Criteria

**A subject will be eligible for inclusion in this study only if ALL of the following criteria apply:**

1. Male and female of any age.
2. Clinically non-infected, corneal persistent epithelial defect (PED) as a result of a severe chemical and/or thermal ocular injury in one or both eyes.
3. [redacted]
4. [redacted]
5. Providing written informed consent and ability to comply with the visit and dosing schedule.

NOTES:

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

## 5.3. Exclusion Criteria

**A subject will not be eligible for inclusion in this study if ANY of the following exclusion criteria apply:**

1. [redacted]
2. Have active clinically significant ocular infection.
3. Subjects with corneal perforation or impending corneal perforation.
4. Subjects with any other past or present ophthalmic disease or medical condition that, in the Investigator's opinion, may affect the safety of the subject or the outcome of the study.
5. Treatment with systemic corticosteroids [redacted]

6. Subjects with severe lid abnormalities as a result of the injury contributory to the persistence of the epithelial defect such as inability to close the lids.
7. Subjects with a history of severe ocular conditions contributory to the persistence of an epithelial defect prior to the injury.
8. Female subjects of childbearing potential who are pregnant, nursing, planning a pregnancy or not using an adequate and medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is a) post-menopausal (defined as at least 12 months of amenorrhea), b) surgically sterilized and at least 3 months post-surgical, or c) using a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide for the duration of the study.
9. Subjects who have participated in an interventional clinical trial within 30 days prior to Day 1.

## 5.4. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regards to safety, the Investigator must refer to the latest edition of the Investigator's Brochure for NEXAGON – Ocular Administration, for detailed information regarding warnings, precautions, contraindications, adverse events and other significant data pertaining to the investigational product being used in this study.

## 5.5. Prior and Concomitant Medications

All medical and surgical treatments/procedures for the PED since the original chemical and/or thermal injury should be recorded and transcribed into the CRF.

A record will be kept of all medication administered, surgical procedures undertaken and supplements used by subjects since the time of injury and PRIOR to study enrollment.

Similarly, over the course of the study FOLLOWING enrollment, a record will be kept of all concomitant medication administered, procedures undertaken and supplements used by subject until study exit will also be recorded. Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication.

For each medication taken or procedure performed, the following information will be collected:

- Medications generic name/procedure name
- Eye that was treated, if applicable
- Indication for the medication/procedure
- Dose, route and frequency of administration of medication
- Date started medication/date of procedure
- Date stopped medication

### 5.5.1. Standard of Care - Topical Ocular Concomitant Medications

Over the course of the study, from baseline assessments through to study completion, subjects will continue to receive the standard of care regimen prescribed to them by their Investigator. The standard of care should remain unchanged until re-epithelialization or study exit if re-epithelialization is not achieved. Details will be recorded on the prior and concomitant medication case report form.

The only exception will be on study days where IP is to be administered. On these days, it is important for the Investigator or delegate to advise the subject [redacted]

**Patching:** Is only required as indicated post application of the investigational product.

[redacted]

Therapy considered necessary to a subject's welfare may be given at the discretion of the Investigator but prior to application this should first be discussed with the Medical Monitor or Sponsor representative.

Systemic standard of care will not be defined by the protocol but by the Investigator's or study site routine practice. However, systemic medications and regimen for the treatment of the PED should remain unchanged for the duration of the study, until re-epithelialization or study exit. Details must be recorded in the source documents and the CRF.

### 5.5.2. Prohibited Medications

Medications to be avoided over the course of the study are:

- [redacted]

- [redacted]

# 6. STUDY ASSESSMENTS AND PROCEDURES

## 6.1. Informed Consent

Written informed consent will be obtained for this study by the Principal Investigator or suitably qualified designee from all subjects before any protocol-specific procedure can be performed.

This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to Good Clinical Practice (GCP). The Investigator must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. All questions about the trial must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. For additional information, please refer to Section 11.3.

## 6.2. Demography

PRIOR to Day 1 when eligibility is being assessed, the following will be collected on the CRF:

- Gender
- Ethnicity
- Race, and
- Date of birth

## 6.3. Urine Pregnancy Test

Urine pregnancy tests will be performed on all female subjects of childbearing potential immediately PRIOR to randomization on Day 1 BEFORE application of investigational product. **The test must be confirmed as negative before randomization.** Another final pregnancy test will be performed when the subject re-epithelizes or when the subject exits the study due to non-healing of the PED or another reason.

In the event of pregnancy, the subject will be withdrawn from the study and the pregnancy will be followed up to term for safety evaluation.

## 6.4. Clinical Laboratory Tests

Routine blood laboratory tests will be performed BEFORE application of investigational product. Baseline blood samples may be done during the Eligibility Assessments OR prior to randomization on Day 1.

These baseline laboratory results will serve as a record for subjects on study entry, enable comparison with results on study exit post treatment (whether healing occurred or not) and enable Investigators to

make an informed assessment of any adverse events or serious adverse events, that may occur during the study.

NO specific laboratory results (other than a positive pregnancy test) will be used to exclude a subject from entry or continued participation in the study, unless in the Investigator's opinion the results indicate the subject has a concurrent condition that may affect the safety of the subject or potentially the outcome of the study (Exclusion Criteria 5).

The same blood tests will be repeated when the subject completes the Treatment Period of the study. Refer to Table 1 - Schedule of Assessments. A sample of up to [redacted] will be collected at each timepoint and the sample prepared as detailed in the Laboratory Manual.

The tests to be performed are as follows:

- [redacted]
- [redacted]

## 6.5. Medical History and Concomitant Medication

A medical history, including details of any ongoing medical conditions, will be recorded PRIOR to Day 1 and before eligibility is confirmed. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to randomization and receiving investigational product treatment. **All medications that are used during a subject's participation in the study must be recorded in the source documents and transcribed onto the CRF.**

## 6.6. Ocular History and Eligibility Assessments Prior to Day 1 and Prior to Randomization Day 1

A detailed ocular examination and history will be conducted **PRIOR to the Day 1 visit** and assessed against the inclusion and exclusion criteria of this protocol. For subjects with a bilateral ocular injury, both eyes should be assessed.

Specific information regarding the etiology and prior history of the PED must be recorded as follows:

- Cause of the defect;
- Date when the defect first appeared (regarded as the first day of injury);
- Medications and/or surgical procedures that have been used to treat the PED, including non-prescription therapies, since injury;
- Measurements of the defect to enable assessment of epithelial defect responsiveness to standard of care;
- Classification of the lesion using the Dua grading scale as detailed in Appendix 1.

Other assessments will include:

- Ocular symptoms questionnaire – to record severity of symptoms
- Ocular Injury - Physician Assessment
- Visual acuity
- Biomicroscopy

- PED assessment including digital photography
- Ophthalmoscopy

**On Day 1, prior to randomization**, the following assessments will include:

- Ocular symptoms questionnaire
- Ocular Injury - Physician Assessment
- Visual acuity
- [redacted]
- PED assessment including digital photography

Refer to Table 1 - Schedule of Assessments for assessments prior to and on Day 1.

[redacted]

## 6.7. Ocular Assessments following Randomization

Once eligibility is confirmed the following assessments will be conducted at all further study visits, unless otherwise specified. If investigational product is to be administered at a study visit, the ocular assessments MUST be conducted PRIOR to investigational product application. In addition, the Ocular Symptoms Questionnaire and Ocular Pain Measurement Rating Scale which both involve subject responses should be conducted before other ocular assessment are conducted by the Investigator or delegate.

[redacted]

### 6.7.1. Ocular Symptoms Questionnaire

The Investigator will query the subject for the severity of the ocular symptoms in the study eye as indicated in Appendix 2. This questionnaire should be conducted before other ocular assessments are performed by the Investigator or delegate.

[redacted]

### 6.7.2. Ocular Pain Measurement Rating Scales

[redacted]

This rating scale should be conducted before other ocular assessments are performed by the Investigator or delegate. Refer to Appendix 3 for details.

[redacted]

### 6.7.3. Ocular Injury - Physician Assessment

The Investigator will assess the injury in the study eye at [redacted] Refer to Appendix 8 for the assessment scale and criteria. [redacted]

### 6.7.4. Slit Lamp Examination

Slit lamp biomicroscopy (without pupil dilation) will be performed during the study on both the study eye treated with investigational product and fellow eye. Observations for the slit lamp biomicroscopy will be graded as detailed in Appendix 5.

### 6.7.5. Measuring the Epithelial Defect and Photography Assessments

The epithelial defect size will be recorded to assess eligibility PRIOR to Day 1 and randomization on Day 1 then at all following visits, as indicated in Table 1: Schedule of Assessments. The cornea will be stained with **fluorescein** prior to measurement.

The size of the PED will be measured:

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

To ensure the corneal epithelium remains undisturbed after randomization, [redacted] Assessment and measurement of the defect size will be done using fluorescein. [redacted]

One drop of lubricant can be used to moisten a fluorescein strip, shaken once, then touched to either the tear film or the inferior fornix. After two to three blinks, photographs can be taken. [redacted]

[redacted] **Extreme care must be taken to avoid physical disruption of the healing epithelium**.

[redacted]

[redacted]

[redacted] photographs may be taken [redacted], *i.e.,* focused and with the entire defect in view, are achieved. Refer to Appendix 6 and Appendix 7 for details.

A separate User's Manual will provide additional instructions on the slit lamp photography to those site personnel responsible for taking the digital images and measuring the PED. All users must also have training on the instructions prior to undertaking any photographs for this study.

[redacted]

### 6.7.6. Visual Acuity

Visual acuity is to be performed in the same manner at each scheduled assessment. Refer to Appendix 4. [redacted]

### 6.7.7. Ophthalmoscopy

If possible, an ophthalmoscopic assessment – [redacted] will be performed with the eye dilated when re-epithelialization occurs or when the subject exits the Treatment Period with an unhealed PED.

[redacted]

### 6.7.8. Intraocular Pressure

Intraocular pressure (IOP) will be assessed in both the study eye and fellow eye only on the days shown in Table 1: Schedule of Assessments.

[redacted]

A final IOP measurement will be taken when the subject exits the study.

The method used to measure IOP, whilst not standardized across study sites, MUST be kept the same for each individual subject within a study site. [redacted]

[redacted]

# 7. INVESTIGATIONAL PRODUCT

## 7.1. Description of the Investigational Product

The investigational product used in the study will be NEXAGON® [redacted] (NEXAGON) formulated at [redacted] and Vehicle 0.0 mg/mL (0%).

NEXAGON is a [redacted] gel for topical ophthalmic application. The investigational product is formulated with sterile, [redacted] All vials are identical in appearance and the vial labels will not identify the contents, *i.e.,* the treatment allocated to a subject will be masked to both the site and other personnel working on this study. Vials will be labeled with codes and it will not be possible to know what the contents of the vials are, unless there is a medical emergency requiring unmasking (refer to Section 7.8).

## 7.2. Dosage

Each investigational product and Vehicle dose application to the study eye will comprise of [redacted]

*No topical ocular drops or ointment standard of care treatment will be permitted* [redacted] *following investigational product administration.*

Investigational product will be applied on [redacted]

## 7.3. Packaging and Labeling

The contents of the investigational product label will be in accordance with all applicable regulatory requirements. Each Investigator will be supplied with sufficient supplies to conduct the trial. Additional study kits treatment packs will be supplied as needed to the site.

The investigational product will be provided to the site packaged in tamper-evident masked study kits. Investigational product is double-masked with neither the Investigator or subject knowing which treatment arm has been allocated.

[redacted] The labels on the primary and secondary containers will not identify the contents.

[redacted] Refer to Section 7.7 Treatment Assignment for further details.

[redacted]

[redacted]

## 7.4. Investigational Product Storage, Handling and Administration

Investigational product will be dispatched to a site only after receipt of required documents in accordance with all regulatory requirements and Amber procedures.

Only subjects enrolled in the study may receive investigational product, in accordance with all regulatory requirements. Investigational product must be dispensed or administered according to procedures described herein.

### 7.4.1. Investigational Product Storage

Investigational product study kits should be maintained [redacted] and must be stored in a secure area, with access limited to the Investigator and authorized site staff.

Each site will be dispatched a pre-determined supply of investigational product study kits and ancillary cartons. Additional study kits and ancillary cartons of investigational product will be supplied as needed.

### 7.4.2. Investigational Product Dispensing – Masked Study Kits

Three treatment groups will be evaluated in this study [redacted]

- GROUP A – [redacted]
- GROUP B – [redacted]
- GROUP C – Vehicle (0%)

Only authorized site staff will be able to dispense and supply investigational product to the study subject. No special safety requirements are required prior to handling the investigational product.

The designee will remove the assigned study kit - the lowest Kit Number in their inventory - from the refrigerator and write the Subject Identifier (ID) on the outer study kit label. The designee must also confirm that the tamper-evident label which seals the study kit is still intact. If the tamper-evident label is voided in any way the kit should be set-aside in the secure storage area and not used. The Study

Monitor should be contacted and a replacement study kit can be organized through the nominated unmasked study statistician.

An intact study kit will be opened on Day 1 of the study, the day of randomization. The designee should remove the vial labelled Day 1 and [redacted] and to ensure that there is no visible damage to the container. If the investigational product container appears to be compromised, it should not be used, but instead returned [redacted]

Once checked and confirmed as being in a good condition, the appropriate vial [redacted]

### 7.4.3. Investigational Product Dispensing – Open-Label Ancillary Cartons

For subjects requiring a [redacted]

### 7.4.4. Investigational Product Administration

No topical ocular drops or ointments standard of care treatment should be applied [redacted] investigational product administration.

When the subject is due to receive investigational product, the vial should be [redacted]

[redacted]

Further details on presentation, storage, administration and accountability will be provided in the study Pharmacy Manual.

## 7.5. Product Accountability

The Investigator is responsible for investigational product accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated staff must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of investigational product received from and returned to Amber, the amount administered to subjects, and the amounts destroyed at the site.

## 7.6. Assigning the Subject Identifier (Subject ID)

Upon signing the informed consent form, each subject will be allocated a unique Subject ID, consisting of a 3-digit study site number and then a 3-digit sequential number corresponding to the order in which subjects **are screened** at that site, *e.g*., 001, 002, 003, *etc*.

The unique Subject ID assigned will be retained by that subject for the duration of their participation in the study.

## 7.7. Treatment Assignment

Subjects will be assigned to one [redacted] treatment arms in accordance with the randomization schedule. [redacted]

## 7.8. Unmasking

The Investigator may unmask a subject's treatment assignment only in the case of an emergency when knowledge of the investigational product is essential for the clinical management or welfare of the subject. [redacted]

If a drug-related serious adverse event (SAE; as defined in Section 9.2: "Definition of an SAE") is reported, the Medical Monitor may unmask the treatment assignment for the individual subject. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the subject's treatment assignment. When applicable, a copy of the regulatory report may be sent to the Investigator in accordance with relevant regulations, Sponsor policy or both.

# 8. SUBJECT COMPLETION AND WITHDRAWAL

## 8.1. Subject Completion

In order to be considered a study completer, subjects must meet the following TWO criteria:

1. Complete the masked Treatment Period until either of the following
    a. Re-epithelialization
    b. Completion of [redacted]
2. Enter and complete the [redacted] Post-healing Follow-up Phase (following re-epithelialization during [redacted] Double Masked Treatment Phase or re-epithelialization during open-label section of the study*).

[redacted]

### 8.1.1. Subject Premature Withdrawal from Study

A subject who is administered investigational product, but who does not complete the study, as defined in Section 8.1, has prematurely discontinued. Prematurely discontinued subjects will not be replaced.

***A subject may voluntarily discontinue participation in this study at any time. The Investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time for safety reasons.***

**In addition, subjects WILL be withdrawn from the study, in consultation with the Medical Monitor and the Investigator, if any of the following criteria are met:**

- A subject is significantly non-compliant with the requirements of the protocol.
- A subject becomes pregnant (NOTE: the pregnancy will be followed up to term for safety follow-up. Relevant safety information collected after the study has completed will be reported as supplemental information).
- [redacted]
- Sponsor discontinues the study.

**Premature withdrawal from the study MAY occur if:**

- A subject is treated with a prohibited medication. This decision will be made by the Medical Monitor in conjunction with the Investigator as to whether premature withdrawal is warranted.
- The condition of the study eye worsens in the opinion of the Investigator and alternative rescue treatment is required.

Subjects who meet the criteria for premature withdrawal, during the Treatment Period will have the [redacted] / Exit Visit performed.

**Subjects who meet the criteria for premature withdrawal, during the Post-healing Follow-up Period will complete all the ophthalmic assessments of the visit where the premature withdrawal criterion was identified, if possible.**

All subjects who exit the study prematurely will have a safety follow-up visit (unscheduled visit) or telephone call scheduled 30 days after their last application of investigational product to assess any AEs/SAEs.

**If a subject is prematurely discontinued from participation in the study for any reason, the Investigator must make every effort to locate and perform all evaluations specified above**.

Any clinically significant adverse events or clinically significant unfavorable changes in the laboratory tests observed during the discontinuation visit will necessitate that the subject be followed or referred for treatment until satisfactory resolution occurs.

In the event that a subject is prematurely discontinued from the study at any time due to an adverse event (AE) (as defined in Section 9.1) or SAE (as defined in Section 9.2), the procedures stated in Section 9 must be followed.

### 8.2. Eligibility Assessment (Screening) Failures

A subject who has at least one study procedure performed (in addition to signing a consent form) and is assigned a Subject ID, but is not randomized, is classified as having failed study entry and deemed a Screen Failure. Subject ID, demography and reason for screen failure will be recorded in the electronic CRF.

## 9. ADVERSE EVENT DEFINITIONS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE), as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this section of the protocol. Country specific safety reporting requirements are detailed further in the Safety Management Plan for the protocol.

### 9.1. Definition of an AE

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily 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 an investigational product whether or not related to the investigational product.

AEs will be recorded from the time of first application of the investigational product and until the final visit.

#### 9.1.1. Treatment Emergent Adverse Event (TEAE)

Treatment emergent AEs (TEAEs), those that occur after the first dose of study medication, are undesirable events not present prior to investigational product treatment, or an already present event that worsens either in intensity or frequency following treatment.

## 9.2. Definition of a SAE

An SAE (experience) or reaction is any untoward medical occurrence that at any dose:

a. Results in death.
b. Is life-threatening and/or sight threatening.
   NOTE: The term "life-threatening" or “sight threatening” in the definition of "serious" refers to an event in which the subject was at risk of death or loss of vision at the time of the event; it does not refer to an event which hypothetically might have caused death or loss of vision if it were more severe.
c. Requires in subject hospitalization or prolongation of existing hospitalization.
   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
d. Results in persistent or significant disability/incapacity.
   NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma, which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events, that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse.

### 9.2.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will be reported as AEs and SAEs.

The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

## 9.3. Assigning Causality

The Principal Investigator or medically qualified Sub-investigator, listed on the FDA Form 1572, must make a determination of the relationship of the AE or SAE to the investigational product using the following categories:

**Definitely related:** This category applies to those AEs that the Investigator feels are incontrovertibly related to the IP. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; and (3) it follows a known response pattern to treatment with IP.

**Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the IP. An adverse event may be considered probable if or when (must meet at least three of the four criteria): (1) it follows a reasonable temporal sequence from application of the IP; (2) it could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) it disappears or ameliorates upon discontinuation of the IP; or (4) it follows a known response pattern to treatment with IP.

**Possibly related:** This category applies to those AEs which, after evaluation are judged unlikely to be related to the IP, but this cannot be ruled out with certainty. An adverse event may be considered possible if or when (must meet at least two of the four criteria): (1) it follows a reasonable temporal sequence from application of IP; (2) it could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) disappears or is decreased upon discontinuation of the IP; or (4) it follows a known response pattern to treatment with IP.

**Unlikely to be related:** In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the IP. An adverse event may be considered unlikely if or when (must meet at least two of the four criteria): (1) it does not follow a reasonable temporal sequence from application of IP; (2) it could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) disappears or is decreased upon removal of the IP; or (4) it does not follow a known response pattern to treatment with IP.

**Unrelated:** This category applies to those adverse events which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, *etc.*) and determined with certainty to have no relationship to the study IP.

This causality assessment must be signed and dated by the person making the evaluation in source documents.

## 9.4. Reporting of SAEs to the Sponsor

SAEs will be reported promptly to the Sponsor (or delegate), as described in the following table, once the Investigator determines that the event meets the protocol definition of an SAE.

| Type of SAE | Initial SAE Reports | | Follow-up Information on a Previously Reported SAE | |
|---|---|---|---|---|
| | Time Frame | Documents | Time Frame | Documents |
| All SAEs | Within 24 hours from first becoming aware | SAE data collection documents | 24 hours | Updated SAE data collection documents |

# 10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The following section is to describe the planned analyses and reporting for this study. It includes a description of the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. Further details and the including the specific statistical methods that will be used are included in the NEX-PED-005 Statistical Analysis Plan (SAP). The statistical analysis methods presented in the SAP will supersede the statistical analysis methods described below.

## 10.1. Study Design Considerations

### 10.1.1. Primary Hypotheses

[redacted]

### 10.1.2. Sample Size Assumptions

[redacted]

## 10.2. Data Analysis Considerations

### 10.2.1. Analysis Populations

[redacted]

[redacted]

### 10.2.2. General Considerations

[redacted]

### 10.2.3. Interim Analysis

A staged interim analysis (IA) will be performed [redacted]

[redacted]

Further details of each stage of the IA are described in NEX-PED-005 Statistical Analysis Plan.

### 10.2.4. Multiplicity Adjustment

[redacted]

### 10.2.5. Baseline Characteristics

Demographic and baseline characteristics such as age, gender, or disease status will be summarized and listed. Medical history, ocular history, and etiology of the PED will also be summarized and listed.

### 10.2.6. Subject Disposition

Subject enrollment, inclusion in analysis populations, and study completion/withdrawal from the study for the main study as well as the open-label section of the study will be summarized and listed.

### 10.2.7. Efficacy Analyses

The primary efficacy outcome will be the comparison of each dose of NEXAGON to Vehicle for:

- The proportion of subjects with corneal epithelial recovery, defined as a cornea that re-epithelializes by [redacted] of treatment and remains re-epithelialized for at [redacted] after initial re-epithelialization was first recorded (during the masked treatment portion of the study).

The secondary efficacy outcomes will be the comparison of each dose of NEXAGON to Vehicle for:

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

The exploratory efficacy outcomes will be the comparison of each dose of NEXAGON to Vehicle for:

[redacted]

using an analysis of covariance model incorporating all three treatment groups and baseline as a [redacted]

### 10.2.8. Safety Analyses

Verbatim descriptions of adverse events (AEs) will be mapped to MedDRA terms and be presented in a data listing. Treatment emergent AEs (TEAEs), those that occur after the first dose of study medication, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Similar summaries will be presented for: related TEAEs, TEAEs by maximum severity, serious TEAEs, and TEAEs leading to test article discontinuation.

Slit lamp biomicroscopy and ophthalmoscopy measures will be summarized [redacted]

Clinical laboratory results will be summarized [redacted]

Summaries of safety measures during the open-label section of the study will be completed similarly, for those subjects entering into the open-label salvage.

# 11. STUDY CONDUCT CONSIDERATIONS

## 11.1. Institutional Review Board / Independent Ethics Committee (IRB/IEC)

The Principal Investigator agrees to provide the IRB/IEC with all appropriate material, including the Investigator's brochure and the subject Information Sheet and Consent Form. The trial will not be initiated until appropriate IRB/IEC approval (as per GCP Essential Documents 8.2.7) of the protocol and the informed consent document have been obtained in writing by the Investigator, and copies have been received by Amber. Appropriate reports including an annual update/report on the progress of the study by the Principal Investigator will be submitted to the IRB/IEC and Amber, in accordance with applicable regulatory requirements and in agreement with policy established by Amber.

## 11.2. Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (see References).

## 11.3. Informed Consent

Properly executed written informed consent, in compliance with the International Conference on Harmonization, and other regulatory requirements (as relevant), shall be obtained from each subject before the subject is entered into the trial or before any unusual or non-routine procedure is performed. Attention will be directed to the basic elements of disclosure that are required for incorporation into the informed consent under GCP 4.8 and/or U.S. Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]), as applicable. Additional elements of informed consent, if appropriate, must be included in the document (21 CFR 50.25[b]).

Sample informed consent documents will be provided to each site. Amber or a representative will review the site informed consent document for inclusion of all required elements prior to submission to the IRB/IEC. Revisions to the approved informed consent must also be reviewed and approved by Amber prior to submission to the IRB/IEC. The final IRB/IEC-approved document must be provided to Amber for regulatory purposes.

The informed consent document must be signed by each subject/legally authorized representative (LAR) before his or her participation in the study. A copy of the signed and dated Informed Consent Form and the Subject Information Sheet must be provided to the subject. If new information related to the study arises, subjects will be asked to sign a revised informed consent document. If applicable, it will be provided in a certified translation of the local language. Signed consent forms must remain in each subject's medical record and must be available for verification by Study Monitors at any time.

The approved Informed Consent Form will be filed at site.

## 11.4. Study Discontinuation

Amber has the right to terminate or suspend this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies that indicates a potential health hazard to subjects;
- Subject enrollment is unsatisfactory;
- Data recording is repeatedly inaccurate or incomplete, i.e., persistent non-compliance with GCP;
- Large numbers of prematurely discontinued subjects;
- Significant protocol violations (i.e., violation of eligibility criteria, dosing errors, and/or missing data for study endpoint analysis).

Compliance with the following is mandatory: GCP 5.21 (Sponsor: Premature Termination or Suspension of a Trial and GCP 4.12 Investigator: Premature Termination or Suspension of a Trial).

## 11.5. Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, Amber must promptly inform the Investigator/institution and the regulatory authority(s) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC must also be informed promptly and provided the reason(s) for the termination or suspension by Amber or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

If the study is prematurely terminated or suspended for any reason, the Investigator/institution must promptly inform the trial subjects, must assure appropriate therapy and follow-up for the subjects, and,

where required by the applicable regulatory requirement(s), must inform the regulatory authority(s). In addition:

- If the Investigator terminates or suspends a trial without prior agreement of Amber, the Investigator must inform the institution where applicable, and the Investigator/institution must promptly inform Amber and the IRB/IEC and must provide Amber and the IRB/IEC a detailed written explanation of the termination or suspension.
- If Amber terminates or suspends a trial (see GCP 5.21), the Investigator must promptly inform the institution where applicable and the Investigator/institution must promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
- If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see GCP 3.1.2 and 3.3.9), the Investigator must inform the institution where applicable, and the Investigator/institution must promptly notify Amber and provide Amber with a detailed written explanation of the termination or suspension.

**The following data and materials are required by Amber before a study can be considered to be complete or terminated:**

All essential documents as detailed in GCP Section 8, including the following:

- Laboratory findings, clinical data and all special test results from screening through the end of the study (including the follow-up period) for all enrolled subjects.
- CRF/Records used in this study. Records (including correction forms) for all enrolled subjects will be properly completed by appropriate study personnel and signed and dated by the Investigator as required.
- Completed investigational product accountability records, investigational product inventory log, and inventory of returned clinical material forms.
- Return of all unused investigational product to Amber, unless an alternate disposal method is agreed upon at study initiation by Amber and investigational site(s).
- Copies of protocol amendments and IRB/IEC approval/notification, if appropriate.
- A summary of the study prepared by the Principal Investigator (IRB/IEC summary closure letter is acceptable).

## 11.6. Study Initiation

Investigator(s) must complete all regulatory documentation as required by local and national regulations.

**Essential documents required for authorization of supply of the investigational product:**

The following documentation must be received by the Amber staff before investigational product is supplied to the site [GCP 5.14.2]:

- Investigator's current CV or Investigator biography with the following details as a minimum:
    - Completed in English
    - The Investigator's name and address
    - Study location address (if different from above)
    - Qualification details

  - Current position(s)
  - Previous professional experience
- All required signatures from site personnel on final approved protocol and any amendment(s).
- IEC/IRB written and dated favorable opinion/approval of the following [GCP 3.3.6]:
  - Protocol
  - Informed consent documents
  - Any other information required by the IEC/IRB for favorable opinion/approval
- Regulatory approval and importation license (where applicable).
- Investigator/Institution agreements [GCP 5.1.4].
- Financial agreements (these may be included in Investigator/Institution Agreement).
- Completed and signed Investigator and Sub-investigators' financial disclosure form in compliance with the Food and Drug Administration (FDA) Financial Disclosure Rule.
- FDA form 1572.

Please refer to GCP Section 8 for full details of essential documents required for the conduct of a clinical trial.

## 11.7. Protocol Deviations

A deviation from the protocol when no amendment has been submitted and approved would be regarded as a protocol violation. All protocol violations must be documented and reported to Amber.

## 11.8. Case Report Forms

Study data will be recorded on electronic Case Report Forms. When electronic CRFs are used, corrections to data will be made according to 21 CFR Part 11, Electronic Records; Electronic Signatures.

## 11.9. Records Retention

The Investigator will maintain all research records, reports, and case history reports for a period of two years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements of if needed by Amber (as per GCP 5.5.11).

It is the policy of Amber that the study data must be verifiable with the source data, which necessitates access to all original recordings, laboratory reports, and subjects' records. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. The subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to enrollment.

## 11.10. Data Handling

Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by Amber or their authorized

representative after descriptive and statistical analyses and reports have been generated and are complete. Data from these forms will be entered into a computerized database, validated, coded using specific dictionaries, and quality-assured. Following the resolution of data questions and queries, a random audit may be performed.

## 11.11. Study Monitoring and Compliance

All aspects of the study will be carefully monitored by Amber or authorized representatives of Amber, according to GCP and standard operating procedures for compliance with applicable government regulations. Access to all records, both during the trial and after trial completion, must be made available to Amber at any time for review and audit to ensure the integrity of the data.

Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. However, ethical reasons may warrant the failure to obtain and record certain data or to record data at the times specified. If data are not recorded per protocol, the reasons must be clearly documented on the CRF/records.

## 11.12. Use of Information and Publications

It is understood by the Investigator that the information generated in this study will be used by Amber in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide Amber with complete test results, all study data, and access to all study records and images, de-identified to protect subject confidentiality.

Amber recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Any results of medical investigations with Amber products and/or publication/lecture/manuscripts based thereon will be exchanged and discussed by the Investigator and Amber representative(s) 30 days before submission for publication or presentation. Due regard shall be given to Amber legitimate interests, *e.g.*, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field and protecting confidential data and information. Amber shall be furnished with a copy of any proposed publication. Comments will be rendered without undue delay and not later than 14 days after requested.

Results from Investigations will not be made available to any third party by the investigating team outside the publication procedure, as outlined previously. Amber will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (*i.e.*, author and reference).

## 11.13. Protocol Amendments

Only Amber may modify the protocol. Protocol amendments will only be made after consultation and agreement between Amber and the Investigator(s). Amendments must be approved by all applicable national and local committees including, but not limited to, the FDA or the Drugs Controller General of India before implementation. The only exception is when an Investigator considers that a subject may be harmed and immediate action is necessary. Under these circumstances, approval by the chairman of the IRB/IEC or an authorized designee must be sought as soon as is practicable. The Investigator must inform Amber and the full IRB/IEC no later than 5 working days after the emergency occurs. Protocol-specified safety reporting requirements must be adhered to independent of any other variables. All amendments that have an impact on subject risk or the study objectives or that require revision of the informed consent document must be approved by the IRB/IEC before implementation. Administrative changes to the protocol and/or changes that do not impact subject safety, risk, or comfort may be implemented prior to IRB/IEC approval if local institutional policy permits.

# APPENDIX 1: [redacted]

[redacted]

[redacted]

# APPENDIX 2: [redacted]

Determine the severity and frequency of each symptom in the study eye (if bilateral injury, also the fellow eye) by questioning the subject with regard to the following:

[redacted]

# APPENDIX 3: [redacted]

At each scheduled visit, the Visual Analogue Scale, below, will be completed by the subject to rate the intensity of the pain being experienced by the subject in the study eye (if bilateral injury, also the fellow eye) at that moment in time.

[redacted]

[redacted]

[redacted]

[redacted]

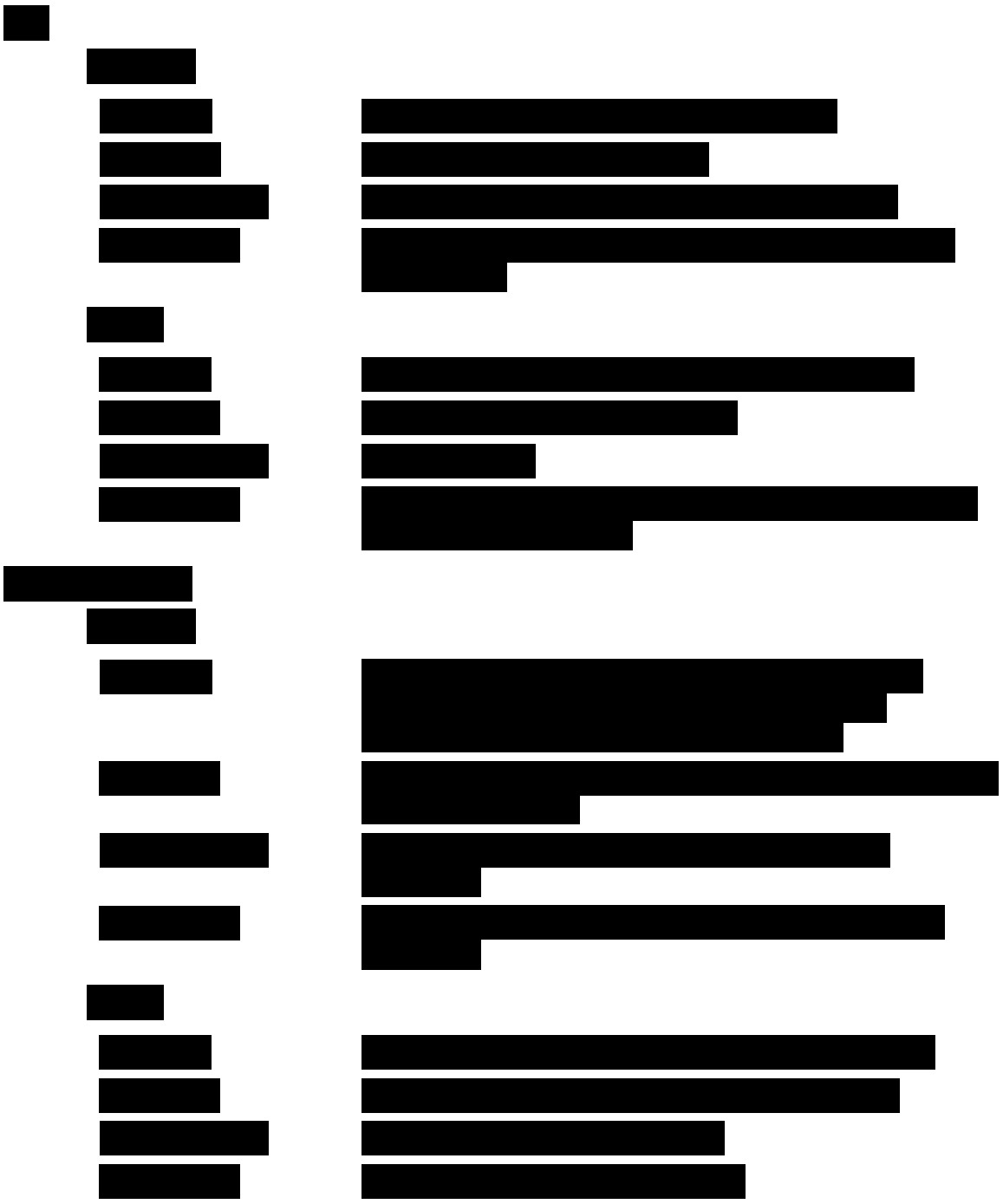
[redacted]

# APPENDIX 4: VISUAL ACUITY AND REFRACTION

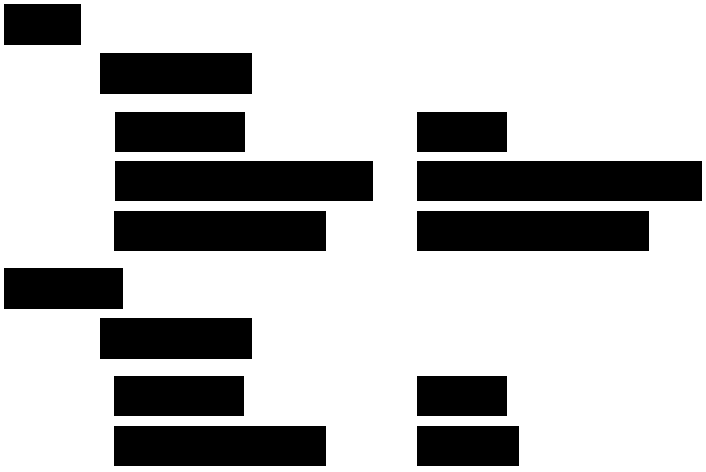
Visual acuity is to be performed in the same manner at each visit. Visual acuity will be assessed using the Snellen Chart. **The test distance and illumination for the chart must be kept constant throughout the study.**

# APPENDIX 5: BIOMICROSCOPY/SLIT LAMP EXAMINATION FOR OCULAR SIGNS

Slit lamp biomicroscopy (without pupil dilation) will be performed during the study on both the study eye treated with investigational product and the fellow eye. Observations for the slit lamp biomicroscopy will be graded as below:



[redacted]



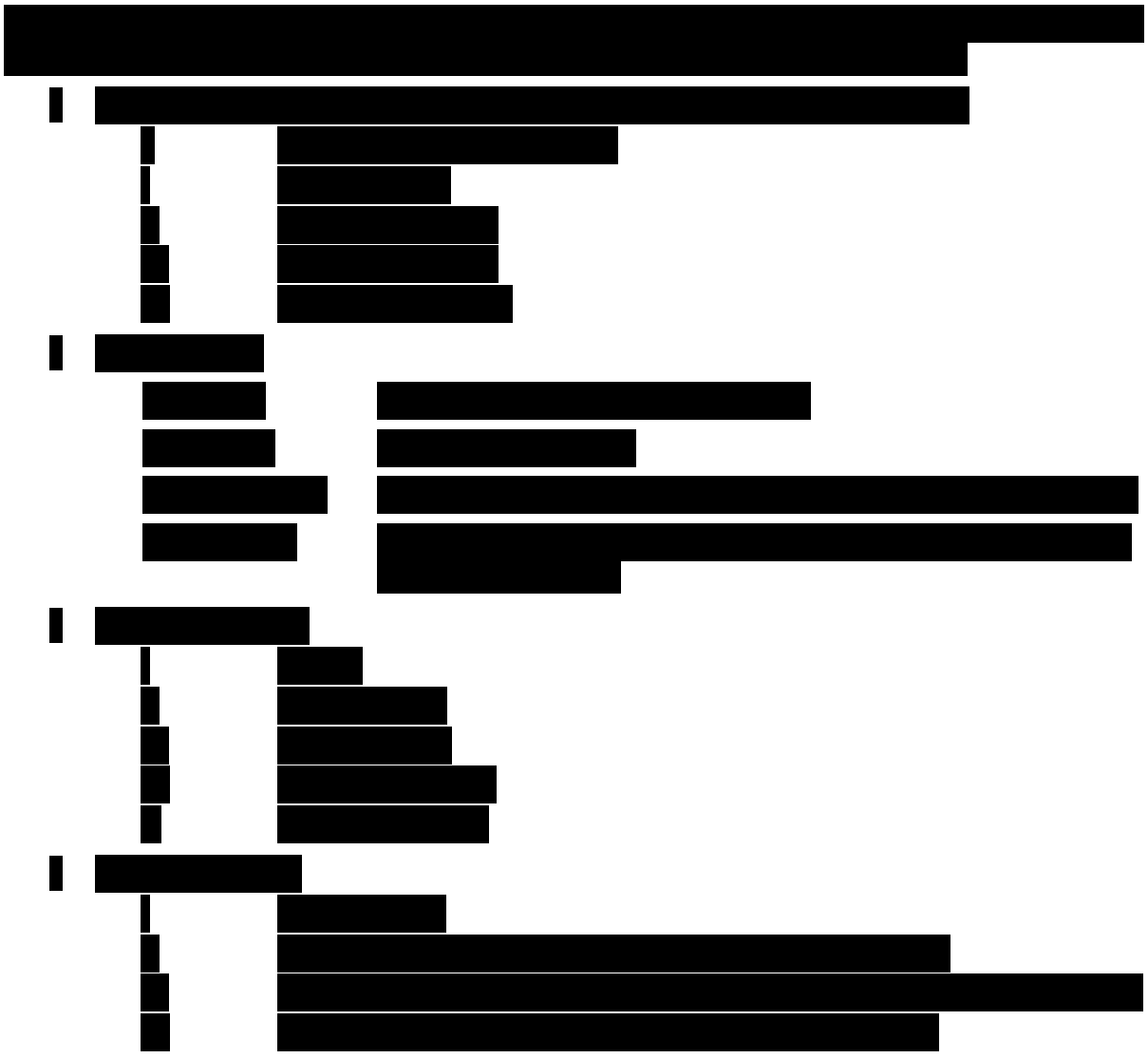
# APPENDIX 6: MEASURING THE EPITHELIAL DEFECT

# APPENDIX 7: SLIT LAMP DIGITAL PHOTOGRAPHY OF THE EPITHELIAL DEFECT

Digital photographs will be taken of the corneal PED during the slit lamp examination. A separate User's Manual will provide additional detailed instructions on the slit lamp photography to those site personnel responsible for taking the digital images. All users must also have training on the instructions prior to undertaking any photographs for this study.

# APPENDIX 8: OCULAR INJURY – PHYSICIAN ASSESSMENT

The Investigator will assess the study eye (if bilateral injury, also the fellow eye) against the following criteria ONLY at the following visits:



# APPENDIX 9: [redacted]

[redacted]

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