formerly

STUDY PROTOCOL # OBG PED-001

A PILOT STUDY OF THE SAFETY AND EFFECTIVENESS OF THE EYEGATE OCULAR BANDAGE GEL, A 0.75% CROSSLINKED HYALURONIC ACID APPLIED TOPICALLY FOR THE IMPROVEMENT OF PERSISTENT CORNEAL EPITHELIAL DEFECTS (PED)

PROTOCOL VERSION DATE: AUGUST 02, 2022
VERSION 02

KIORA PHARMACEUTICALS, INC.
1371 EAST 2100 SOUTH
SUITE 200
SALT LAKE CITY, UT 84105

I have read and agree to follow the procedures as outlined in this protocol.

_____ _____
Signature of Investigator *Date*

CONFIDENTIALITY AGREEMENT

This protocol contains confidential proprietary information with respect to Kiora Pharmaceuticals, Inc. products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three (3) years after the completion of the study, or until said information shall become a matter of public knowledge or until a formal written agreement for that purpose has been entered into by the parties.

_____
Print Name of Investigator

_____ _____
Signature of Investigator *Date*

A PILOT STUDY OF THE SAFETY AND EFFECTIVENESS OF THE EYEGATE OCULAR BANDAGE GEL, A 0.75% CROSSLINKED HYALURONIC ACID APPLIED TOPICALLY FOR THE IMPROVEMENT OF PERSISTENT CORNEAL EPITHELIAL DEFECTS (PED)

Medical Monitor:	Victor Perez, M.D. Medical Consultant to Kiora Pharmaceuticals, Inc. Mobile: +1 786-390-1292 vlperezmdpa@gmail.com
Chief Development Officer:	Eric Daniels, MD, MBA Kiora Pharmaceuticals, Inc. 1371 East 2100 South Suite 200 Salt Lake City, UT 84105
Investigator:	Enrique Graue, M.D. Instituto de Oftalmología Fundación Conde de Valenciana Chimalpopoca 14 Colonia Obrera México City Mexico Telephone: +52 55-5442-1727

TABLE OF CONTENTS

A PILOT STUDY OF THE SAFETY AND EFFECTIVENESS OF THE EYEGATE OCULAR BANDAGE GEL, A 0.75% CROSSLINKED HYALURONIC ACID APPLIED TOPICALLY FOR THE IMPROVEMENT OF PERSISTENT CORNEAL EPITHELIAL DEFECTS (PED)
PROTOCOL OBG PED-001

SYNOPSIS

STUDY NUMBER	**OBG PED-001**
STUDY TITLE	**A PILOT STUDY OF THE SAFETY AND EFFECTIVENESS OF THE EYEGATE OCULAR BANDAGE GEL, A 0.75% CROSSLINKED HYALURONIC ACID APPLIED TOPICALLY FOR THE IMPROVEMENT OF PERSISTENT CORNEAL EPITHELIAL DEFECTS (PED)**
SPONSOR	Kiora Pharmaceuticals, Inc, Salt Lake City, UT, United States (formerly EyeGate Pharmaceuticals, Inc., Waltham, MA, United States)
INVESTIGATIONAL DEVICE	Crosslinked Thiolated Carboxymethyl Hyaluronic Acid 0.75% (CMHA-S)
STUDY OBJECTIVE	The objective of this study is to evaluate the safety and effectiveness of topical Ocular Bandage Gel (OBG) in patients with persistent corneal epithelial defects (PED). Ocular Bandage Gel (OBG) will be administered six (6) times per day while awake for 4 weeks. The primary exploratory effectiveness outcome for this study is the percentage of patients achieving corneal healing (<0.5 mm lesion size) as determined by corneal fluorescein staining and photos. The effectiveness endpoint will be evaluated by a reader using digital photography of fluorescein stained slit lamp photos.
STUDY DESIGN	This is a prospective, exploratory study in which up to 10 patients (up to 20 eyes [minimum of 10 eyes]) diagnosed with Stage 1 and Stage 2 PED (as defined by fluorescein staining of the cornea and refractory to one or more conventional non-surgical treatments of at least 2 weeks) will receive OBG with a dosing regimen of six (6) times per day over 4 weeks (Sacchetti 2014). Both eyes are to be included if both eyes meet inclusion criteria and both eyes will be treated with OBG. When only one eye meets all eligibility criteria only that eye can be enrolled into the study. The fellow eye can be treated per the investigator's discretion, but the site will provide the subject with careful instruction so that study treatment is applied appropriately and only to the study eye. Study assessments do not need to be done on the fellow eye at future study visits after non-eligibility is determined. Patients will self-administer all treatments. All subjects will be followed through the 4-week study with follow-up visits at Week 1 (± 1 day), Week 2 (± 2 days), Week 3 (± 2 days), and Week 4 (± 2 days).
CLINICAL SITE	Instituto de Oftalmología Fundación Conde de Valenciana, Ciudad de México, Mexico
STUDY POPULATION	Up to 10 patients diagnosed with a persistent corneal epithelial defect (PED) in at least one eye.

NUMBER OF SUBJECTS	Up to 20 eyes (minimum 10 eyes) of 10 patients diagnosed with PED as defined by fluorescein staining of the cornea and refractory to one or more conventional non-surgical treatments of at least 2 weeks. Only one eye is required to qualify in order to be randomized into the study. In the event that a patient is enrolled with both eyes affected, both eyes will be entered as study eyes and followed for safety and effectiveness.
ELIGIBILITY CRITERIA	**Eligible eyes** must meet all of the study criteria listed; exams will be conducted on eligible eyes at all time-points. **Inclusion Criteria** • Patients 18 years of age or older. • Patients with persistent corneal epithelial defects (PED) (Stage 1 and Stage 2 PED). • Patients with PED in one or both eyes, at least one eye meeting all study criteria. • Have PED of at least 2 weeks' duration refractory to one or more conventional non-surgical treatments for Stage 1 and Stage 2 PED (i.e., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops). o Patients can continue with antibiotic and corticosteroid eye drops, if corticosteroid eye drops are no more than twice daily (BID). o There is no objective clinical evidence of improvement in the PED within the 2 weeks prior to study enrollment. • Are willing to maintain a stable dose of any topical ocular treatment in the affected eye(s) during the study treatment period. • Are able to provide written informed consent prior to the start of any study procedures. • Able to return for all study visits at approximately the same time of day and willing to comply with all study-related instructions. **Exclusion Criteria** • Have any active ocular infection (bacterial, viral, fungal or protozoal) in the affected eye(s). • Schirmer's test without anesthesia ≤ 3 mm/ 5 minutes in the affected eye(s). • Patients who have received amniotic membrane transplantation and have not healed. • Have anticipated need for punctal occlusion during the study treatment period. Patients with punctal occlusion or punctal plugs inserted prior to the study are eligible for enrollment if the punctal occlusion or punctal plugs are maintained during the study. • Patients treated with a bandage contact lens but have not healed. • Prior surgical procedure(s) for the treatment of PED (e.g., complete tarsorrhaphy, conjunctival flap, etc.) in the affected eye(s). Patients previously treated with Botox® (botulinum toxin) injections used to induce pharmacologic blepharoptosis are eligible for enrollment only if the last injection was given at

	least 90 days prior to enrollment in the study and no injections are planned during the study. • Patients with lid abnormalities including entropion, ectropion, lagophthalmos, Bell's palsy or inadequate lid closure and lid margin scarring, etc. • Corneal disease that may affect outcomes including keratoconus, forme fruste keratoconus, severe limbal stem cell deficiency, pellucid marginal degeneration, contact lens warpage, and/or herpes keratitis. • Stage 3 PED or evidence of corneal ulceration, corneal melting or perforation in the affected eye(s). Stage 3 PED is defined as those characterized by corneal ulcer with stromal involvement that may be complicated by stromal melting and progression to corneal perforation (Sacchetti 2014). • Use of medications that may affect and/or decrease the rate of corneal healing [e.g., systemic and or topical medications (corticosteroids more than 2 drops per day and antimetabolites such as mitomycin) and/or antiviral medications] and or recent use (within the past 6 months) of isotretinoin, amiodarone, or any medications that can affect corneal integrity. • Presence or history of any ocular or systemic disorder or condition that might hinder the effectiveness of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or be judged by the investigator to be incompatible with the study visit schedule or conduct (e.g., progressive or degenerative corneal or retinal conditions, uveitis, optic neuritis, poorly controlled diabetes, autoimmune disease, systemic infection, neoplastic diseases). Diabetes is not an exclusion for study entry as long as the patient is under stable control and no medication changes are required during the duration of the study. • Have moderate and/or severe blepharitis and/or meibomitis requiring a change in treatment in either eye in the past 30 days prior to screening (mild or moderate blepharitis and/or meibomitis is permitted if on stable therapy, such as lid hygiene and/or oral Omega 3 fatty acids [FAs], for at least 30 days prior to screening and is not expected to change for the duration of the trial). • Ocular surgery not allowed during the study treatment period. • Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein). • If on oral and/or inhaled steroids and/or immunomodulators at screening and expecting changes in dose and/or frequency anytime during the trial. • Participation in another clinical trial at the same time as this study or use of any investigational agent within 4 weeks of Baseline visit.
STUDY DURATION	All subjects will be followed through the four (4) week study (Day 28 ±2 days).
SCHEDULE OF VISITS	All subjects will be examined at Baseline and then return to the clinic for examination at: Week 1 (± 1 day), Week 2 (± 2 days), Week 3 (± 2 days), and Week 4 (± 2 days).

STUDY PROCEDURES	Study subjects will be instructed to administer the investigational Ocular Bandage Gel 6 times per day for the 4 week treatment period. All subjects will be instructed to return the investigational study product to the site at the Week 4 visit (Day 28 ±2 days).
RESCUE	If a subject being treated with OBG deteriorates such that there is an increase in the PED lesion size ≥ 1 mm and/or progression in lesion depth to corneal melting or perforation and/or onset of infection, the investigator is to discontinue the study treatment as appropriate and rescue the patient as appropriate per the discretion of the investigator. Rescued subjects will be followed to Week 4 for safety purposes and not discontinued from study assessments.
STUDY ASSESSMENTS	Clinical assessments are listed below. Ocular assessments will be conducted in enrolled eyes. • Concomitant medications • Adverse events (AEs) • Visual Analogue Scale (VAS) • Schirmer's test with anesthetic • Non-invasive tear film break up time (NI-BUT) • Uncorrected Visual Acuity (UCVA) • Slit lamp biomicroscopy • Fluorescein Staining of the Cornea
STUDY OUTCOMES	The exploratory effectiveness endpoints in this study are as follows: • Percentage of patients achieving corneal healing (<0.5 mm lesion size) of the PED determined by corneal fluorescein staining at Week 4. The effectiveness endpoint will also be evaluated by a reader using digital photography of fluorescein stained slit lamp photos. • Time to complete corneal healing (<0.5 lesion size) • Investigator global evaluation of effectiveness at Week 4 The following safety assessments will be collected in both eyes of each subject and the outcomes summarized: • Slit Lamp biomicroscopy • UCVA • AEs • VAS Ocular assessments are bilateral at the Baseline visit (Day 0) when both eyes have a PED and are done in eyes that meet study eligibility (unilateral or bilateral at subsequent visits depending on study eligibility determination at Baseline).

STATISTICAL METHODS	**Sample Size Justification:** The sample size estimations were not based on formal statistical hypotheses testing due to the exploratory nature of this study. **Statistical Analysis:** Descriptive statistics will be used for reporting all available study results. Baseline and demographic characteristics will be documented.

1. INTRODUCTION AND BACKGROUND

DESCRIPTION OF PERSISTENT CORNEAL EPITHELIAL DEFECTS (PED)

Persistent corneal epithelial defects (PED) can be defined as a loss of the integrity of the corneal surface and or a defect in the epithelium, caused by injury or disease, which does not heal by itself within the usual time frame (usually defined as within 14 days) but persists for weeks or even months (Jeng 2011a). Several underlying disease states may result in PED. Nonhealing corneal epithelial defects may also occur after ocular surgery or other physical injuries and/or trauma to the cornea. These defects can be especially troublesome and difficult to heal in diabetics. These nonhealing defects can lead to corneal ulcers, corneal scarring, and opacification and result in visual loss (Lu 2001).

Corneal epithelial wound healing or re-epithelization is a highly regulated process that involves the reorganization, migration, and proliferation of epithelial cells from the limbal stem cells (Dua 2000, Rama 2010). Rapid re-epithelialization of the injured area is extremely important in reducing the risk of microbial superinfection and corneal opacification. Delays in this process may result in corneal scarring, ulceration, and opacification. Compounds that can accelerate wound closure and activate this highly regulated process are of interest because of their major potential benefit for patients with persistent epithelial damage from dry eye, surgical and non-surgical trauma, refractive interventions, corneal abrasion, nonhealing corneal ulcers and neurotrophic corneas secondary to diabetes, cranial nerve palsies, and herpetic keratitis (Lu 2001).

There is an unmet medical need for a therapy that could help heal the cornea. The current standard of care to help re-epithelialize a cornea are “bandage” methods and include aggressive lubricants, debridement and patching, applying a bandage contact lens, human amniotic membrane, use of autologous serum as a supernatant to provide necessary growth factors, suturing the lids via a tarsorrhaphy, or in severe cases applying a conjunctival graft over the cornea (Blackmore 2010, Meller 2011, Young 2004, Jeng 2011b, Pakarinen 1987, Thoft 1977). These are attempts to cover the corneal epithelial defect and allow the cells to migrate in and heal. With autologous serum, the attempt is to capture and apply naturally occurring growth factor and “healing proteins” from one’s own bodily fluids. However, none are effective universally. Often these PED cases recur and end up being costly to the patients and the healthcare provider.

Agents that can accelerate wound closure by increasing the migration and proliferation of corneal epithelial cells are of interest because of their potential benefit for patients with persistent epithelial damage. Patients with PED could benefit significantly from such a topical preparation that could allow the healthy limbal cells to migrate and heal.

1.2 UNDERLYING DISEASES WITH PERSISTENT CORNEAL EPITHELIAL DEFECTS*

Persistent corneal epithelial defects (PED) is a condition that has a duration of less than one year. Underlying disease states that may result in such defects include exposure keratopathy, limbal stem cell deficiency, previous herpes simplex or herpes zoster infection, diabetic keratopathy, neurotrophic keratopathy following corneal transplant surgery, diabetic vitrectomy, and severe dry eye states (McCulley 1993, Jeng 2011a).

Exposure Keratopathy
Exposure keratopathy is the result of incomplete lid closure (lagophthalmos) that causes drying of the cornea despite normal tear production. Among the causes of exposure keratopathy are cranial nerve palsy, aneurysm, herpes infection, and lid malposition. No prevalence data on exposure keratopathy in the U.S. were identified.

Limbal Stem Cell Deficiency
Limbal stem cell deficiency is a disease in which the stem cell functions of the limbus and the barrier function of the limbus fail. Because of failure of corneal epithelial healing from limbal stem cells, as a result of either loss or dysfunction, corneal epithelial defects appear and fail to heal normally (Ahmad 2012).

Herpes Simplex
The incidence of ocular herpes simplex in the U.S. is 20.7 per 100,000 person-years and the prevalence is 149 per 100,000 persons (Liesegang 2001, Young 2004). Corneal complications in patient with herpes simplex are of two main types: epithelial keratitis is inflammation of the cells that form the surface layer of the cornea, and stromal keratitis is inflammation of the middle layer (stroma) of the cornea. The effects of herpes simplex stromal keratitis include scarring, tissue destruction, neovascularization, glaucoma, and persistent epithelial defects. Of the ocular herpes simplex cases in the U.S., 72% of cases had corneal-epithelial involvement (Liesegang 1989).

Herpes Zoster
Herpes zoster ophthalmicus, or ocular shingles, is a rash that involves the nerve that innervates the skin around the upper eyelid, forehead, and scalp (Hall 2003). Neurotrophic keratitis can be the end result of decreased corneal sensation from herpes zoster virus-mediated destruction, including susceptibility to mechanical trauma, decreased lacrimation, and delayed epithelial healing. The incidence of herpes zoster ophthalmicus in the U.S. is 40,000 to 60,000 cases per year. Twenty-five (25%) to 50% of these cases have ocular involvement, 16% of which develop neurotrophic keratopathy (Shaikh 2002).

Diabetic Keratopathy
Diabetic keratopathy has been estimated to occur in 47-64% of diabetic patients during the course of their disease, and diabetics have an increased risk of developing epithelial fragility corneal epithelial defects, recurrent epithelial erosions, decreased sensitivity, abnormal wound healing, increased susceptibility to injury, and non-healing or infected corneal ulceration (Schultz 1981, Abdelkader 2011). Recurrent corneal erosions in patients with diabetes are usually post traumatic and the result of apparently mild epithelial breakdown following cataract or vitreoretinal surgery (Jeganathan 2008). Neuropathic keratopathy is an uncommon complication of diabetes but it can cause corneal ulceration (Lockwood 2006).

Neurotrophic Keratopathy
Neurotrophic keratopathy is a degenerative disease of the corneal epithelium resulting from impaired corneal innervation. A reduction in corneal sensitivity or complete corneal anesthesia is the hallmark of this disease and is responsible for producing epithelial keratopathy, ulceration, and perforation (Bonini 2003). It is most commonly due to herpes infection, chemical injury, or trauma. No data were identified concerning the prevalence of PED in patients with neurotrophic keratopathy. The potential prevalence of PED in patients with neurotrophic keratopathy is included in the prevalence numbers estimated for patients with herpes infection and corneal burns.

Corneal Transplantation
The number of corneal transplants (also referred to as keratoplasty, penetrating keratoplasty, or corneal graft) in 2011 was equal to 46,081 (Eye Bank Association of America®). The incidence of corneal PED following corneal transplants is 16.4% (Rumelt 2008).

Diabetic Vitrectomy
In the U.S. 250,000 vitrectomy surgeries are performed annually with an estimated 25% to 53% performed for diabetics (Virata 1999). The frequency of epithelial debridement during diabetic vitrectomy is 17.4%

(Friberg 2003). Corneal epithelial defects were found in 22.8% of eyes at 2 weeks after corneal epithelial debridement during diabetic vitrectomy (Chen 2009).

Severe Dry Eye States
Persistent corneal epithelial defects (PED) can occur in mucin-deficient dry eye states in patients with Stevens-Johnson syndrome or ocular cicatricial pemphigoid or in patients with lacrimal gland dysfunction such as Sjögren's disease. The prevalence of dry eye disease in the U.S. among men older than 50 is 3.9-7.6% and among women is 5.7% in women less than 50 years of age to 9.8% among women 75 years of age or older (Schaumberg 2009, Schaumberg 2003).

Corneal Burns
The incidence of ocular trauma is 3.1 cases per 1,000 person-years (Wong 2000). Chemical or thermal burns are involved in 7.7% to 18% of all ocular traumas (Kuckelkorn 2002). Approximately 20% of all ocular burns result in PEDs.

*Citation for **Section 1.2** (Wirostko 2015).

2. THE OCULAR BANDAGE GEL

The Ocular Bandage Gel is a stand-alone device that acts as a barrier that minimizes mechanical lid friction and mechanically protects the ocular surface thereby reducing repeat injury and providing an environment that enables the body to repair the ocular surface whether the corneal epithelial defects are large or small. Unlike a semi-rigid film, the Ocular Bandage Gel has an optimized viscosity as a sterile liquid gel which allows it to be administered to the eye from a dropper bottle and is intended for up to six (6) daily applications. The Ocular Bandage Gel is designed to be optically clear with application on the eye and the product is provided sterile in a preservative free multi-dose dropper bottle for commercialization.

2.1 COMPOSITION AND PROPERTIES OF THE OCULAR BANDAGE GEL

OBG is being evaluated in an ongoing pivotal study for the acceleration of re-epithelization of corneal epithelial defects following photorefractive keratectomy (PRK). It is also the subject of a pilot study for dry eye patients with punctate epitheliopathies (PE). The OBG consists of a cross-linked thiolated carboxymethyl hyaluronic acid (CMHA-S) that is designed to resist degradation, thus prolonging the dwell time on the ocular surface of upwards of 2 hours (**EyeGate data).** The viscosity of the OBG has been shown to aid in ocular wound repair by acting as a mechanical moisture barrier and offering physical protection (Chen 1999, Wirostko 2014, Yang 2010).

The OBG is presently available commercially as a veterinary device, manufactured by SentrX Animal Care (Salt Lake City, UT) and sold in the U.S. by Bayer Animal Health as Remend® Corneal Repair (0.75% concentration), indicated for use in the management of superficial corneal ulcers and Remend® Eye Lubricating Drops (0.40% concentration) for the treatment of dry eye in dogs and cats (Williams 2013, Williams 2014, Williams 2017). The product has been used for more than seven years in dogs, cats and horses, with an excellent safety profile and has been shown to manage non-healing corneal wounds and improve dry eye (Williams 2017). The composition of the corneal repair veterinary product is identical to that of the OBG.

3. COMPLETED Clinical Performance studies

The well-controlled studies conducted by EyeGate (EYEGATE-031, EYEGATE-033, EYEGATE-034 for PRK, and OBG PE-041 and OBG PE-042 in PE) demonstrate Ocular Bandage Gel safety and effectiveness to protect the ocular surface and facilitate healing of corneal epithelial defects associated with ocular surface disorders following surgery and related to non-traumatic indications like PEs. In these clinical trials EyeGate evaluated two patient populations, both with recognized ocular surface pathology that could be objectively assessed for meaningful improvements, i.e., closure of large epithelial defects post-PRK surgery and improvement in corneal staining in dry eye subjects with PE.

In five (5) clinical studies, conducted in the U.S., EyeGate has collected data on 368 eyes from 194 subjects that have been exposed to OBG as a stand-alone device. See **Table 1** below. These 368 eyes (194 subjects) include 234 eyes (117 subjects) in the EYEGATE-034 pivotal study, 60 eyes (30 subjects) in the EYEGATE-033 study, 24 eyes (12 subjects) in the EYEGATE-031 study, 30 eyes (15 subjects) in the OBG PE-041 study, and 20 eyes (20 subjects) in the OBG PE-042 study. The OBG arms have demonstrated no safety concerns with excellent tolerability where OBG has been administered a minimum of 4 times/day with applications up to 28 days.

3.1 SUMMARY

The clinical data generated to date serve to help support the safety and effectiveness of the Ocular Bandage Gel for use in managing and improving the signs and symptoms of various epithelial defects. Initial safety and effectiveness findings following use of the Ocular Bandage Gel in subjects who had undergone PRK were very encouraging, with no significant safety concerns and evidence of earlier corneal re-epithelialization than artificial tears and a bandage contact lens.

TABLE 1: OVERVIEW OF OCULAR BANDAGE GEL CLINICAL STUDIES

	EYEGATE-031	EYEGATE-033 (IDE G170117/ A003)	EYEGATE-041 (G180104/ S001)	EYEGATE-033 (IDE G170117/ S001/ A001)	EYEGATE-042 (G180104/ S004)
STUDY DESIGN	Randomized, prospective, multicenter, pilot	Randomized, masked (Reading Center), prospective, multicenter, pilot	Randomized, single-masked (investigator), prospective, multicenter, pilot	Randomized, masked (Reading Center), prospective, multicenter, pivotal	Randomized, masked, prospective, multicenter, pilot
REGION	U.S.	U.S.	U.S.	U.S.	U.S.
STUDY POPULATION	Post-keratectomy patients undergoing PRK	Post-keratectomy patients undergoing PRK	Punctate epitheliopathies (PE)	Post-keratectomy patients undergoing PRK	Punctate epitheliopathies (PE)
DURATION OF STUDY	14-day treatment with follow-up for an additional 14 days, total of 28 days	14-day treatment and follow-up	28-day treatment and follow-up	14-day treatment and follow-up	14-day treatment and follow-up
TREATMENT ARMS	3 (2 active + 1 control)	3 (2 active + 1 control)	2 (1 active + 1 control)	2 (1 active + 1 control)	2 (1 active + 1 control, each eye of every subject)
SUBJECTS (EYES)	N=39 (78)	N=45 (90)	N=30 (60)	N=234 (468)	N=20 (40)
OBG	1. OBG applied 4x/day OU for 2 weeks after surgery in combination with bandage contact lens N=14 (28) 2. OBG stand-alone 4x/day OU for 2 weeks after surgery without bandage contact lens N=12 (24)	1. OBG applied 8x/day OU for 72 hours (3 days) then 4x/day for an additional 11 days after surgery N=15 (30) 2. OBG applied 4x/day OU for 2 weeks after surgery N=15 (30)	• OBG 4x/day OU for 4 weeks N=15 (30)	• OBG 4x/day OU until complete re-epithelialization N=117 (234)	• OBG 4x/day for 2 weeks N=20 (20)
CONTROL ARM	• BCL plus application of artificial tears 4x/day N= 13 (26) • BCL was discontinued once complete re-epithelialization had occurred.	• BCL plus application of artificial tears 4x/day N=15 (30) • BCL was discontinued once complete re-epithelialization had occurred.	• Bausch + Lomb Sensitive Eyes® Rewetting Drops 4x/day for 4 weeks N=15 (30)	• BCL OU until complete re-epithelialization N=117 (234)	• Refresh PF 4x/day for 2 weeks N=20 (20)

	EYEGATE-031	EYEGATE-033 (IDE G170117/ A003)	EYEGATE-041 (G180104/ S001)	EYEGATE-033 (IDE G170117/ S001/ A001)	EYEGATE-042 (G180104/ S004)
STUDY EYE	• Both eyes received the treatment or control per study assignment • Right eye of each subject was defined as the study eye for effectiveness analyses • Both eyes of each subject were included in the safety analyses	• Both eyes received the treatment or control per study assignment • Right eye of each subject was defined as the study eye for effectiveness analyses • Both eyes of each subject were included in the safety analyses	• Both eyes received the treatment or control per randomized assignment • Eye with the greater NEI staining score was the study eye. If the score was the same, the right eye was used	• Both eyes received the treatment or control per randomized assignment • One eye designated as masked study eye for statistical purposes	• One eye received the treatment, and the contralateral eye received the control per randomized assignment
STUDY PROCEDURE	• See above for treatment regimen • The BCL was removed once the cornea was re-epithelialized on slit lamp exam • All study subjects were followed for a total of 28 days	• See above for treatment regimen • The BCL was removed once the cornea was considered re-epithelialized on slit lamp exam • All study subjects were followed for a total of 14 days	• See above for treatment regimen • All study subjects were followed for a total of 28 days	• See above for treatment regimen • OBG was discontinued or BCL was removed once the cornea was re-epithelialized on slit lamp exam • All study subjects were followed for a total of 14 days	• See above for treatment regimen • All study subjects were followed for a total of 14 days
ASSESSMENTS	• Slit lamp measurements • BCVA • IOP • Fundus exam • AEs	• Slit lamp measurements • Photographs of the epithelial defect until healed • Photos evaluated in masked reading center • BCVA • IOP • PRO tool: SPEED™ questionnaire • AEs	• NEI scale corneal staining score • Slit lamp measurements • BCVA • IOP • PRO tool: SPEED™ questionnaire • AEs	• Slit lamp measurements • Photographs of the epithelial defect until healed • Photos evaluated and defect measured at masked reading center • BCVA • UCVA • IOP • Indirect Ophthalmoscopy • PRO tool: SPEED™ questionnaire • AEs	• NEI scale corneal staining score • OSI • HOA • Corneal Topography • TFBUT • VBUT • Slit lamp measurements • BCVA • IOP • PRO tool: SPEED™ questionnaire • AEs

AE= Adverse events, BCL= Bandage contact lens (Acuvue® Oasys® plano lens), BCVA= Best Corrected Visual Acuity, IOP= Intraocular Pressure, NEI= National Eye Institute , OBG= Ocular Bandage Gel, OSI= Ocular Scatter Index, PE= Punctate Epitheliopathies, PRK= Photorefractive Keratectomy, , PRO= Patient-reported Outcome, Refresh PF= Refresh Plus® Preservative Free, SPEED™= Standardized Patient Evaluation of Eye Dryness Questionnaire, TFBUT= Tear Film Break Up Time, UCVA= Uncorrected Visual Acuity, U.S.= United States, VBUT= Vision Break Up Time

4. OBG PED-001

4.1 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of topical Ocular Bandage Gel (OBG) in patients with persistent corneal epithelial defects (PED). Ocular Bandage Gel (OBG) will be administered six (6) times per day while awake for 4 weeks.

The primary exploratory effectiveness outcome for this study is the percentage of patients achieving corneal healing (<0.5 mm lesion size) as determined by corneal fluorescein staining and photos. The effectiveness endpoint will be evaluated by a reader (using digital photography of fluorescein stained slit lamp photos.

4.2 STUDY DESIGN

This is a prospective, exploratory study in which up to 10 patients (up to 20 eyes [minimum of 10 eyes]) diagnosed with Stage 1 and Stage 2 PED (as defined by fluorescein staining of the cornea and refractory to one or more conventional non-surgical treatments of at least 2 weeks) will receive OBG with a dosing regimen of six (6) times per day over 4 weeks (Sacchetti 2014).

Both eyes are to be included if both eyes meet inclusion criteria and both eyes will be treated with OBG. When only one eye meets all eligibility criteria only that eye can be enrolled into the study. The fellow eye can be treated per the investigator's discretion, but the site will provide the subject with careful instruction so that study treatment is applied appropriately and only to the study eye. Study assessments do not need to be done on the fellow eye at future study visits after non-eligibility is determined.

Patients will self-administer all treatments. Study subjects will be instructed to administer the investigational Ocular Bandage Gel 6 times per day for the 4 week treatment period. All subjects will be followed through the 4-week study with follow-up visits at Week 1 (± 1 day), Week 2 (± 2 days), Week 3 (± 2 days), and Week 4 (± 2 days). All subjects will be instructed to return the investigational study product to the site at the Week 4 visit (Day 28 ±2 days).

If a subject being treated with OBG deteriorates such that there is an increase in the PED lesion size ≥ 1 mm and/or progression in lesion depth to corneal melting or perforation and/or onset of infection, the investigator is to discontinue the study treatment as appropriate and rescued at the discretion of the investigator. Rescued subjects will be followed to Week 4 and not discontinued from study assessments.

4.3 STUDY OUTCOMES

The exploratory effectiveness endpoints in this study are as follows:

- Percentage of patients achieving corneal healing (<0.5 mm lesion size) of the PED determined by corneal fluorescein staining at Week 4. The effectiveness endpoint will also be evaluated by a reader using digital photography of fluorescein stained slit lamp.
- Time to complete corneal healing (<0.5 lesion size)
- Investigator global evaluation of effectiveness at Week 4

The following safety assessments will be collected in both eyes of each subject and the outcomes summarized:

- Slit Lamp biomicroscopy
- UCVA
- AEs

- VAS

Ocular assessments are bilateral at the Baseline visit (Day 0) when both eyes have a PED and are done in eyes that meet study eligibility (unilateral or bilateral at subsequent visits depending on study eligibility determination at Baseline).

4.4 STUDY POPULATION

Up to 10 patients diagnosed with a persistent corneal epithelial defect (PED) in at least one eye. The study will be conducted, and all subjects will be enrolled and assessed at Instituto de Oftalmología Fundación Conde de Valenciana, Ciudad de México, Mexico.

4.5 ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Are able to return for all study visits at approximately the same time of day and willing to comply with all study-related instructions.
- Patients 18 years of age or older.
- Patients with persistent corneal epithelial defects (PED) (Stage 1 and Stage 2 PED).
- Patients with PED in one or both eyes, at least one eye meeting all study criteria.
- Have PED of at least 2 weeks' duration refractory to one or more conventional non-surgical treatments for Stage 1 and Stage 2 PED (i.e., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops).
  - Patients can continue with antibiotic and corticosteroid eye drops if corticosteroid eye drops are no more than twice daily (BID).
  - There is no objective clinical evidence of improvement in the PED within the 2 weeks prior to study enrollment.
- Are willing to maintain a stable dose of any topical ocular treatment in the affected eye(s) during the study treatment period.
- Are able to provide written informed consent prior to the start of any study procedures.
- Are able to return for all study visits at approximately the same time of day and willing to comply with all study-related instructions.

EXCLUSION CRITERIA

- Have any active ocular infection (bacterial, viral, fungal or protozoal) in the affected eye(s).
- Schirmer's test without anesthesia ≤ 3 mm/ 5 minutes in the affected eye(s).
- Patients who have received amniotic membrane transplantation and have not healed.
- Have anticipated need for punctal occlusion during the study treatment period. Patients with punctal occlusion or punctal plugs inserted prior to the study are eligible for enrollment if the punctal occlusion or punctal plugs are maintained during the study.
- Patients treated with a bandage contact lens but have not healed.
- Prior surgical procedure(s) for the treatment of PED (e.g., complete tarsorrhaphy, conjunctival flap, etc.) in the affected eye(s). Patients previously treated with Botox® (botulinum toxin) injections used

to induce pharmacologic blepharoptosis are eligible for enrollment only if the last injection was given at least 90 days prior to enrollment in the study and no injections are planned during the study.

- Patients with lid abnormalities including entropion, ectropion, lagophthalmos, Bell's palsy or inadequate lid closure and lid margin scarring, etc.
- Corneal disease that may affect outcomes including keratoconus, forme fruste keratoconus, severe limbal stem cell deficiency, pellucid marginal degeneration, contact lens warpage, and/or herpes keratitis.
- Stage 3 PED or evidence of corneal ulceration, corneal melting or perforation in the affected eye(s). Stage 3 PED is defined as those characterized by corneal ulcer with stromal involvement that may be complicated by stromal melting and progression to corneal perforation (Sacchetti 2014).
- Use of medications that may affect and/or decrease the rate of corneal healing [e.g., systemic and or topical medications (corticosteroids more than 2 drops per day and antimetabolites such as mitomycin) and/or antiviral medications] and or recent use (within the past 6 months) of isotretinoin, amiodarone, or any medications that can affect corneal integrity.
- Presence or history of any ocular or systemic disorder or condition that might hinder the effectiveness of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or be judged by the investigator to be incompatible with the study visit schedule or conduct (e.g., progressive or degenerative corneal or retinal conditions, uveitis, optic neuritis, poorly controlled diabetes, autoimmune disease, systemic infection, neoplastic diseases). Diabetes is not an exclusion for study entry as long as the patient is under stable control and no medication changes are required during the duration of the study.
- Have moderate and/or severe blepharitis and/or meibomitis requiring a change in treatment in either eye in the past 30 days prior to screening (mild or moderate blepharitis and/or meibomitis is permitted if on stable therapy, such as lid hygiene and/or oral Omega 3 fatty acids [FAs], for at least 30 days prior to screening and is not expected to change for the duration of the trial).
- Ocular surgery not allowed during the study treatment period.
- Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein).
- If on oral and/or inhaled steroids and/or immunomodulators at screening and expecting changes in dose and/or frequency at any time during the trial.
- Participation in another clinical trial at the same time as this study or use of any investigational agent within 4 weeks of Baseline visit.

5. STUDY PROCEDURES

5.1 INFORMED CONSENT

The study will be discussed and the informed consent document (ICD) will be reviewed with each prospective subject by the investigator or a trained clinical professional. Once the subject has been informed of all aspects of the study, the subject will be given a choice to voluntarily confirm participation in the study as documented by completion of the Informed Consent. After signing the ICD and any other applicable local documentation, the site can then proceed with the screening evaluation.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. Subjects are deemed Screen Failures if upon signing the ICD they subsequently fail to meet the eligibility criteria.

The investigator must retain the original, signed written ICD. A copy of the written ICD must be given to the subject.

5.2 SCREENING EVALUATION

After signing the ICD, all potential subjects will undergo an initial screening on Day 0 (Baseline) to determine study eligibility. Ten (10) subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study.

This is a prospective, exploratory study in which up to 10 patients (up to 20 eyes [minimum of 10 eyes]) diagnosed with Stage 1 and Stage 2 PED (as defined by fluorescein staining of the cornea and refractory to one or more conventional non-surgical treatments of at least 2 weeks) will receive OBG with a dosing regimen of six (6) times per day over 4 weeks (Sacchetti 2014)..

Both eyes are to be included if both eyes meet inclusion criteria and both eyes will be treated with OBG. When only one eye meets all eligibility criteria only that eye can be enrolled into the study. The fellow eye can be treated per the investigator's discretion, but the site will provide the subject with careful instruction so that study treatment is applied appropriately and only to the study eye. Study assessments do not need to be done on the fellow eye at future study visits after non-eligibility is determined.

5.3 SUBJECT ID NUMBER

A 3-digit subject identification (SubjID) number will be assigned at the clinical site during Screening and be used to identify the subject throughout their participation. The first digit of the SubjID number will be the site number which will be "1" for this study. The last 2 digits of the SubjID number will be a sequential number, using a leading "0", according to an individual site's enrollment. For example, the seventh subject screened will have a SubjID number of "1-07".

The SubjID number and patient initials are to be recorded on all study documents and will link the study documents to the patient's name and medical record. To maintain confidentiality, the patient's name should not be recorded on any study document other than the ICD. This is an open-label study and there is no randomization or other identifying number.

5.4 SCREEN FAILURE

The study site will document all screen failures on the Subject Screening/Enrollment Log with the coded reason (by Inclusion or Exclusion number) for not enrolling the subject. Collected screen failure baseline visit data for demographics and non-eligibility will be entered onto study CRFs and screen failure ICDs and source documents will be made accessible by the site during site monitoring visits.

5.5 INVESTIGATIONAL TREATMENT ADMINISTRATION

Subjects will be screened at Baseline (Day 0) to determine eligibility. Eligible study subjects will be instructed to administer the investigational Ocular Bandage Gel 6 times per day for the 4 week treatment period.

- **Treatment:** Ocular Bandage Gel 6 times per day for 28 days (4 weeks). Treatment will be in both eyes only if both eyes meet all study eligibility criteria

At Baseline (Day 0) the investigator will dispense Ocular Bandage Gel to the subject. If only one eye is eligible for the study the investigator or study coordinator will review which eye to administer the study treatment. The subject will be given one (1) sterile, preservative free multi-dose dropper bottle of Ocular Bandage Gel. Subjects will be given a Patient Instructions document to refer to for Ocular Bandage Gel self-administration. The site will observe the patient apply Ocular Bandage Gel in their eye(s) at the Baseline visit. After the Baseline visit subjects will administer the study treatment at home and document all applications and application times using a study Patient Diary provided by the site. At each visit the study coordinator will review the study Patient Diary. Subjects will need to bring all the study eye drops with them at all visits. If for any reason a patient loses or damages their bottle of OBG during the study, they should contact the site to obtain a replacement as soon as possible so that no or minimal doses are missed. Missed or late applications will be documented in the Patient Diary. Subjects will return used and unused bottles of Ocular Bandage Gel to the study coordinator at the Day 28 visit.

On study visit days there should be at least two (2) hours between the last OBG instillation and the visit.

5.6 RESCUE

If a subject being treated with OBG deteriorates such that there is an increase in the PED lesion size ≥ 1 mm and/or progression in lesion depth to corneal melting or perforation and/or onset of infection, the investigator is to discontinue the study treatment as appropriate and rescue the patient as appropriate per the discretion of the investigator. Rescued subjects will be followed to Week 4 for safety purposes and not discontinued from study assessments.

5.7 SCHEDULE OF VISITS

There are a total of five (5) study visits starting with the Baseline (Day 0) visit. Participating subjects will return to the clinic for examination on Week 1 (Day 7 ± 1 day), Week 2 (Day 14, ± 2 days), Week 3(Day 21, ± 2 days), and Week 4 (Day 28, ± 2 days). Study exit is done at the Week 4 visit. Clinic visits should occur around the same time of day (i.e. all visits in the morning or all visits in the afternoon). On study visit days there should be at least two (2) hours between the last OBG instillation and the visit.

5.8 STUDY ASSESSMENTS

Clinical assessments are listed below. Ocular assessments will be conducted in enrolled eyes. Sites will capture the time that each assessment is done.

- Concomitant medications
- AEs
- VAS
- External ocular exam
- Schirmer's test with anesthetic
- NI-BUT
- UCVA
- Slit lamp biomicroscopy
- Fluorescein Staining of the Cornea
- Corneal photo with fluorescein

Baseline Visit (Day 0)

The following procedures will be performed. Ocular assessments will be conducted bilaterally.

- Informed consent (signed ICD will be obtained before any study assessments are undertaken)
- Collection of demographic data
- Documentation of medical/ophthalmic history
- Record of concomitant medications
- VAS
- External ocular exam
- Schirmer's test with anesthetic
- NI-BUT
- UCVA
- Slit lamp biomicroscopy
- Fluorescein staining of the Cornea
- Fluorescein photos of staining taken in triplicate and sent to the reader
- Study enrollment for eligible patients
- Dispensation of Ocular Bandage Gel and review of Patient Diary completion
- If applicable, schedule subject for Week 1 visit

Week 1 (Day 7 ±1 day)

The following procedures will be performed. Ocular assessments will be conducted bilaterally On study visit days there should be at least two (2) hours between the last OBG instillation and the visit.

- Record of concomitant medications (new and updates)
- Assess for AEs
- NI-BUT
- UCVA
- Slit lamp biomicroscopy
- Fluorescein staining of the Cornea
- Fluorescein photos of staining taken in triplicate and sent to the reader
- Review of entries in Patient Diary
- Schedule subject for Week 2 visit

Week 2 (Day 14 ±2 days)

The following procedures will be performed. Ocular assessments will be conducted bilaterally. On study visit days there should be at least two (2) hours between the last OBG instillation and the visit.

- Record of concomitant medications (new and updates)
- Assess for AEs
- VAS
- NI-BUT
- UCVA
- Slit lamp biomicroscopy
- Fluorescein staining of the Cornea
- Fluorescein photos of staining taken in triplicate and sent to the reader

- Review of entries in Patient Diary
- Schedule subject for Week 3 visit

Week 3 (Day 21 ±2 days)

The following procedures will be performed. Ocular assessments will be conducted bilaterally. On study visit days there should be at least two (2) hours between the last OBG instillation and the visit.

- Record of concomitant medications (new and updates)
- Assess for AEs
- NI-BUT
- UCVA
- Slit lamp biomicroscopy
- Fluorescein staining of the Cornea
- Fluorescein photos of staining taken in triplicate and sent to the reader
- Review of entries in Patient Diary
- Schedule subject for Week 4 visit

Week 4 (Day 28 ±2 days)

The following procedures will be performed. Ocular assessments will be conducted bilaterally. On study visit days there should be at least two (2) hours between the last OBG instillation and the visit.

- Record of concomitant medications (new and updates)
- Assess for AEs
- VAS
- External ocular exam
- Schirmer's test with anesthetic
- NI-BUT
- UCVA
- Slit lamp biomicroscopy
- Fluorescein staining of the Cornea
- Fluorescein photos of staining taken in triplicate and sent to the reader
- Investigator global evaluation of effectiveness
- Collection of and review of entries in Patient Diary

5.9 UNSCHEDULED VISITS

An Unscheduled Visit case report form (CRF) shall be completed from source data gathered at the time the subject is examined. Additional examinations may be conducted as necessary to ensure the safety and well-being of subjects during the study period. The CRFs will be completed for each unscheduled visit or assessment that the subject completes between scheduled study visits. **Table 2** provides an overview of all activities to be conducted during the clinical study.

TABLE 2: SCHEDULE OF VISITS AND ASSESSMENTS*

Procedures	Baseline Day 0	Week 1 (± 1 day)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)
Informed consent	X				
Confirm eligibility**	X				
Medical and Ophthalmic history	X				
Concomitant Medication Review	X	X	X	X	X
Adverse events	X	X	X	X	X
VAS	X		X		X
Schirmer's Test with anesthetic	X				X
NI-BUT	X	X	X	X	X
UCVA	X	X	X	X	X
External Ocular Examination	X				X
Slit Lamp Exam	X	X	X	X	X
Corneal staining with fluorescein	X	X	X	X	X
Corneal Photos with fluorescein	X	X	X	X	X
Dispensation of OBG and provision of Study Treatment Diary	X				
Site review of Study Treatment Diary		X	X	X	X
Investigator global evaluation of effectiveness					X

***Whenever possible, all clinic visits should occur around the same time of day for that individual (i.e., all visits in the morning or all visits in afternoon)**
****Confirmation of eligibility includes collection of demographics, review of all Inclusion/Exclusion criteria**
NI-BUT= Non-invasive tear break up time, OBG= Ocular Bandage Gel, UCVA= Uncorrected visual acuity, VAS= Visual analog scale

5.10 SUBJECT WITHDRAWAL

All subjects have the right to withdraw at any point during the treatment without prejudice. The investigator can discontinue any subject at any time if continued participation in the study would result in harm to the subject. All efforts should be made by the investigator to retain the patient in the study. If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) the subject discontinued themselves from the study. The reason must be recorded in the subject's file and on the End of Study Form and emailed to Kiora Pharmaceuticals, Inc.

5.11 LOST TO FOLLOW-UP SUBJECTS

Subjects who do not return for follow-up must be contacted to ask that they return for the visit. For those subjects who cannot be reached, at least three (3) telephone or email attempts should be made and documented. If there is still no response, the subject will be considered lost-to-follow-up unless there is a further communication by the subject.

5.12 PROTOCOL MODIFICATIONS AND DEVIATIONS

Protocol modifications may be introduced during the study. Prior to implementation of any protocol modifications, a protocol amendment will be submitted and cleared by the local Ethics Committee.

Any deviations from this protocol intended to protect the life or physical well-being of a subject in an emergency are to be reported to Kiora Pharmaceuticals, Inc. as well as the local Ethics Committee as soon as possible, and no later than 5 working days after the emergency occurred.

All protocol deviations will be documented on a Protocol Deviation CRF.

6. DATA HANDLING AND RECORDKEEPING

6.1 SUBJECT ACCOUNTABILITY

All subjects randomized in this clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects who have been enrolled in the investigation, including subjects whose study treatment was discontinued early, have reached the final study visit.

6.2 CONFIDENTIALITY

All medical records associated with the clinical investigation will be made available for review by Kiora Pharmaceuticals personnel, its qualified designee and governmental/regulatory agencies involved. The results of the study may be published in the future for scientific and marketing purposes, but the identity (name) of each subject will not be revealed. All records will be stored in a secure area by the investigator, the designee, and at Kiora Pharmaceuticals, Inc.

6.3 SOURCE DATA AND CASE REPORT FORMS

Source documents and paper CRFs (3 part carbonless paper) will be utilized to collect data during this clinical investigation. Source document forms and CRFs are to be maintained and stored by the investigator. All CRF entries must be made in black or blue ink and changes must be made by strike-through only with date and initials or signature. No "white-out" is to be used on the source documents or CRFs. At the end of the trial the original CRFs will remain onsite and the monitor or sponsor will retrieve the bottom 2 pages.

6.4 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

Each shipment of investigational product will include a packing list that will give the amount shipped and the lot numbers. This packing list must be reconciled by the investigational site with the contents of the shipment and then complete the accountability logs for the Kiora Ocular Bandage Gel. All investigational products at the site must be

stored in a secured/locked area at room temperature. Product reconciliation activities will also be conducted periodically in conjunction with site monitoring visits.

The investigator must maintain accurate records of the receipt of all study products shipped to the site, including the date and lot numbers received with the use of the appropriate accountability log. The receipt, dispensation, and return of the treatment product and control products will be recorded on the logs. Investigational product can only be dispensed to eligible study subjects.

Subjects should return all unused and used Ocular Bandage Gel to the clinic site on Week 4.

6.5 RECORD RETENTION

Clinical sites are to retain any and all clinical trial material (documentation, photographs, etc.) for a period of two years from the date the marketing application is approved or two years after the investigation has been discontinued and the local Ethics Committee notified, or as directed by their institutional document retention requirements, whichever is the longest. After that time, the items may be returned to Kiora Pharmaceuticals for archiving. Unused medical products are to be destroyed on site at the conclusion of the enrollment period. Destruction will be documented.

7. EVALUATION OF SAFETY

Safety will be assessed by determining the incidence and severity of AEs, as well as BCVA findings, and slit lamp findings.

Safety outcomes include:

- UCVA findings
- Slit lamp findings
- AEs
- VAS

Ocular assessments are bilateral at the Baseline visit (Day 0) when both eyes have a PED and are done in eyes that meet study eligibility (unilateral or bilateral at subsequent visits depending on study eligibility determination at Baseline).

Throughout the course of the proposed study, all efforts will be made to document possible AEs or untoward findings. If an AE occurs, the first concern will be the safety of the subject. Appropriate medical intervention will be made. Any AEs observed by the investigator or reported by the subjects, regardless of severity and whether or not it is ascribed to the investigational device, will be recorded.

7.1 ADVERSE EVENT DEFINITIONS

An AE is any untoward and unintended sign, symptom or disease temporally associated with the use of an investigational device or other protocol-imposed intervention, regardless of the suspected cause. Conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF. Changes in a chronic condition of disease that are consistent with natural disease progression are NOT AEs and also should not be recorded on the AE pages of the CRF. Collection of AEs begins at the time of consent.

7.1.1 Serious Adverse Events (SAE)

An AE should be classified as an SAE and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE places the subject at immediate risk of death)

- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)
- It is considered sight-threatening by the investigator.

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

7.1.2 Unanticipated Adverse Device Effects (UADEs)

An unanticipated adverse device effect (UADE) are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence. Anticipated AEs are identified in **Section 7.4**. Unanticipated adverse device effect (UADEs) also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Any sight-threatening event, whether listed in the protocol or not, is considered to be reportable as a UADE. Any subject presenting with an active AE at the last study visit should be followed until resolution of the AE or until the condition is stable with no expected change

7.2 ADVERSE EVENT ASSESSMENT

All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded using standard medical terminology. The onset date, end date, severity, action(s) taken, relationship to test article and/or device, and outcome of all AEs will be documented in the CRFs. The investigator must assess and record in the source documents and CRFs whether the event is related to the test article, device and/or procedure. Subjects with an AE should be followed to determine outcome.

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

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If more than one distinct AE occurs, each event should be recorded separately.

However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the CRFs rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension ⇒fainting and fall to floor ⇒head trauma ⇒neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

7.3 CLASSIFICATION OF ADVERSE EVENTS

7.3.1 Intensity/Severity

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

Mild:	Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities.
Moderate:	Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.
Marked:	Considerable discomfort with limitation in daily activities, some assistance usually required; medical intervention/therapy usually required.
Severe:	Extreme discomfort and limitation in daily activities, significant assistance required; ***significant*** medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a SAE.

7.3.2 Relatedness

The study investigator, in conjunction with the sponsor, will evaluate if the AE is related to the investigational device. Relationship is defined in the following manner:

Not related: Evidence indicates no plausible direct relationship to the study device, such that:

- A clinically plausible temporal sequence is inconsistent with the onset of the AE and device administration; and/or
- A causal relationship is considered biologically implausible
- The AE can be attributed to concurrent/underlying illness, other drugs, or procedures.

Related: Evidence indicates a reasonable temporal sequence of the event with the study device administration exists, or that the association of the event with study device administration is unknown and the event is not reasonably supported by other conditions, such that:

- There is a clinically plausible time sequence between onset of the AE and study treatment administration; and/or
- There is a biologically plausible mechanism for study treatment causing or contributing to the AE; and
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures.

7.3.3 Expectedness

All AEs will be evaluated as to whether they are expected or unexpected.

Expected (anticipated): An adverse event is expected when the nature, severity, or degree of incidence was previously described.

Unexpected (unanticipated): An adverse event is unexpected when the nature, severity, or degree of incidence was not previously described.

7.3.4 Outcome

The clinical outcome of an AE will be characterized as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death

7.3.5 Treatment or Action Taken

- None
- Treatment Taken
- Hospitalization
- Study Device Discontinued
- Subject Withdrawn

7.4 ANTICIPATED ADVERSE EVENTS

Anticipated AEs include those that might reasonably be expected to occur in this study because they are associated with the indication, PE, with the Ocular Bandage Gel, the Refresh PF eye drops or the eye exam procedures. Data collection will include a forced recording of anticipated AEs. A list of anticipated AEs is provided below, as follows:

Ocular Bandage Gel

- Redness of the eye
- Discomfort in the eye
- Allergic reaction
- Temporary blurred vision
- Temporary burning/sting/irritation
- Tearing and/or epiphora

Eye Exams and fluorescein eye drops

- Discomfort in the eye
- Temporary blurred vision due to the drops, lights and photos
- Temporary change in vision
- Eye irritation and or burning and or redness
- Temporary burning and/or stinging from the eye drops used to assess the corneal changes and to be used with the photographs and to measure the intraocular pressure

7.5 REPORTING SAES AND UNANTICIPATED ADVERSE DEVICE EFFECTS

All SAEs and UADEs will be reported to the sponsor and the medical monitor by e-mail to the addresses below:

edaniels@kiorapharma.com and **vlperezmdpa@gmail.com**

The report should be made as soon as possible but no later than 24 hours after the investigator first learns of the SAE and no later than five (5) working days after the investigator first learns of the UADE. If required per local Ethics Committee guidelines, a report should be sent by the site to the ethics committee in the time required per the committee. An UADE should be documented as an AE using the Adverse Event CRF and then also documented on the ADE/UADE form. All AEs should be documented by completing the AE CRF.

8. MONITORING PLAN

Kiora Pharmaceuticals personnel or qualified designee will monitor the study in a manner consistent with applicable health authority regulations and the clinical research standards adopted by Kiora Pharmaceuticals. Study monitoring will involve the following elements:

- Kiora Pharmaceuticals personnel or designee meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.
- Kiora Pharmaceuticals personnel or designee meet with the investigator(s) at the time the site begins to enroll in order to ensure that subjects are being properly selected and that study data are being correctly recorded.
- Kiora Pharmaceuticals personnel or designee visit the clinical site at any time during the study to review and/or collect the CRFs.
- Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

9. STATISTICAL PLAN

9.1 STATISTICAL ANALYSES

Descriptive statistics will be used for reporting all available study results. Baseline and demographic characteristics will be documented.

9.2 SAMPLE SIZE

The sample size estimations were not based on formal statistical hypotheses testing due to the exploratory nature of this study.

10. GOOD CLINICAL PRACTICE STATEMENT

This study will be conducted in accordance with the protocol, good clinical practice (GCP) guidelines and all applicable international and local regulatory requirements.

11. BIBLIOGRAPHY

Abdelkader H, Patel DV, McGhee CN, Alany RG. New therapeutic approaches in the treatment of diabetic keratopathy: a review. Clin Exper Ophthalmol. 2011 ;39 :259–270.

Ahmad S. Concise review: limbal stem cell deficiency, dysfunction, and distress. Stem Cells Trans Med. 2012;1:110–115.

Blackmore SJ. The use of contact lenses in the treatment of persistent epithelial defects. Cont Lens Anterior Eye. 2010;33:239–244.

Bonini S, Rama P, Lambiase A. Neurothropic keratitis. Eye. 2003;17:989–995.

Chen WL, Lin CT, Ko PS Yeh PT, Kuan YH, Hu FR, et al. In vivo confocal microscopic findings of corneal wound healing after corneal epithelial debridement in diabetic vitrectomy. Ophthalmol. 2009;116:1038–1047.

Dua HS, Azuara-Blanco A. Limbal stem cells of the corneal epithelium. Surv Ophthalmol. 2000;44:415–425.

Friberg TR., Ohji M Scherer JJ, Tano Y. Frequency of epithelial debridement during diabetic vitrectomy. Am J Ophthalmol. 2003;135:553–554.

Hall JH. Herpes zoster ophthalmicus. American Uveitis Society. 2003; 1–4.

Jeganathan VSE, Wang JJ, Wong TY. Ocular associations of diabetes other than diabetic retinopathy. Dia Care 2008;31:1905–1912.

Jeng BH Treating the nonhealing epithelial defect. CRS Today Europe. 2011a.

Jeng BH. Use of autologous serum in the treatment of ocular surface disorders. Arch Ophthalmol. 2011b;129:1610–1612.

Liesegang TJ Melton LJ 3rd, Daly PJ, Ilstrup DM. Epidemiology of ocular herpes simplex incidence in Rochester, Minn, 1950 through 1982. Arch Ophthalmol. 1989;107:1155–1159.

Liesegang TJ. Herpes simplex virus epidemiology and ocular importance. Cornea. 2001;20:1–13.

Lockwood A, Hope-Ross M, Chell P. Neurotrophic keratopathy and diabetes mellitus. Eye. 2006;20:836–839.

Lu L, Reinach PS, Kao WW. Corneal epithelial wound healing. Exp Biol Med. 2001;226:653–664.

McCulley JP, Horowitz B, Husseini ZM Horowitz M. (1992). Topical fibronectin therapy of persistent corneal epithelial defects. Fibronectin Study Group. Trans Am Ophthalmol Soc. 1992;91:367-386, discussion 386–390.

Meller D, Pauklin M, Thomasen H, Westekemper H, Steuhl KP. Amniotic membrane transplantation in the human eye. Dtsch Arztebl Int. 2011;108:243–248.

Novack GD, Asbell P, Barabino S, et al. TFOS DEWS II Clinical Trial Design Report. Ocul Surf. 2017; 15(3):629–649.

Pakarinen M, Tervo T, Tarkkanen A. Tarsorraphy in the treatment of persistent corneal lesions. Acta Ophthalmol Suppl. 1987;182:69–73.

Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, Pellegrini G. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010; 363: 147–155.

Rumelt S, Bersudsky V, Blum-Hareuveni T, Rehany U. Persistent epithelial defects and ulcers in repeated corneal transplantation: incidence, causative agents, predisposing factors and treatment outcomes. Graefes Arch Clinic Exp Ophthalmol. 2008;246:1139–1145.

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571–579.

Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among U.S. women. Am J Ophthalmol. 2003;136:318–326.

Schaumberg DA, Dana R. Sullivan DA, Buring JE. Prevalence of dry eye disease among U.S. men: Estimates from the Physician's Health Studies. Arch Ophthalmol. 2009;127:763–768.

Schultz RO, Van Horn DL, Peters MA, Klewin KM, Schutten WH. Diabetic keratopathy. Trans Am Ophthalmol Soc. 1981;79:180–199.

Shaikh S, Ta CN. Evaluation and management of Herpes zoster ophthalmicus. Am Fam Physician. 2002;66:1723–1730.

Thoft RA. Conjunctival transplantation. Arc Ophthalmol. 1977;95:1425–1427.

Virata SR, Kylstra JA, Singh HT. Corneal epithelial defects following vitrectomy surgery using hand-held, sew-on, and noncontact viewing lenses. *Retina* (Philadelphia, PA) 1999;19(4):287–290.

Williams DL, Mann BK. A Crosslinked HA-based hydrogel ameliorates dry eye symptoms in dogs. International J Biomaterials 2013: Article ID 460437.

Williams DL and Mann BK. Efficacy of a crosslinked hyaluronic acid-based hydrogel as a tear film supplement: A masked controlled study. PLoS One. 2014; 9(6).

Williams DB, Wirostko, Mann B. Topical cross-linked HA-based hydrogel accelerates closure of corneal epithelial defects and repair of stromal ulceration in companion animals. Invest Ophthalmol Vis Sci. 2017;58:4616–4622.

Wirostko B, Mann BK, Williams DL, Prestwich GD. Ophthalmic uses of a thiol-modified hyaluronan-based hydrogel. Adv Wound Care. 2014 Nov 1;3(11):708–716.

Wirostko B, Rafii M, Sullivan DA, Morelli J, Ding J. Novel therapy to treat corneal epithelial defects: a hypothesis with growth hormone. Ocul Surf. 2015;13(3):204–212.

Wong TY, Klein BE, Klein R. The prevalence and 5-year incidence of ocular trauma. The Beaver Dam Eye Study. Ophthalmol. 2000;107:2196–2202.

Yang G, Espandar L, Mamalis N, Prestwich GD. A crosslinked hyaluronan gel accelerates healing of corneal epithelial abrasion and alkali burn injuries in rabbits. Vet Ophthalmol 2010;13:144–150.

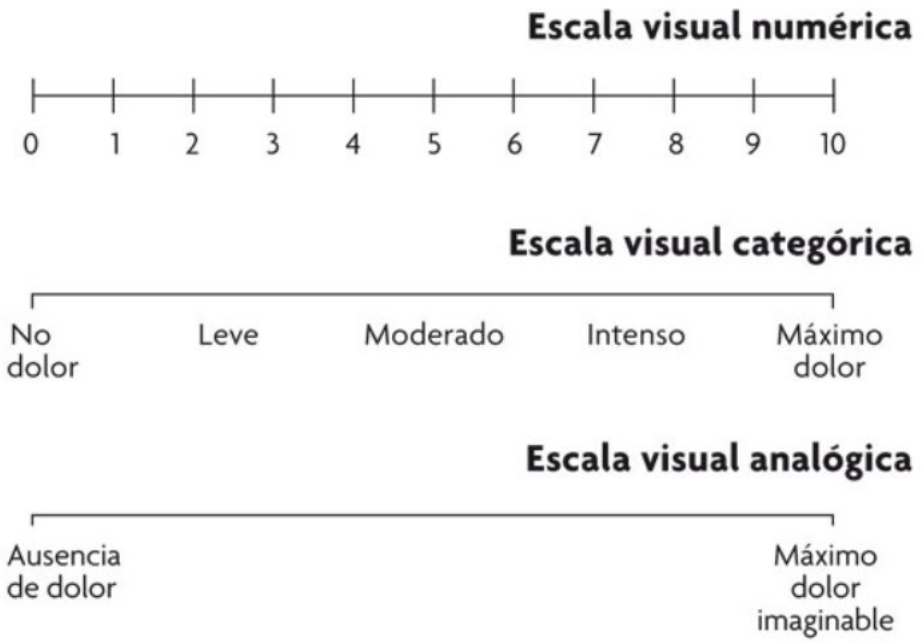
Young AL, Cheng ACO, Ng HK, Cheng LL, Leung GYS, Lam DSC. The use of autologous serum tears in persistent corneal epithelial defects. Eye. 2004;18: 609–614.

12. APPENDIX 1: EXAMINATION PROCEDURES

12.1 VISUAL ANALOG SCALE (VAS)

A VAS will be provided to subjects at visits indicated in **Table 2**. The VAS is used in this study to determine the pain intensity experienced by individuals. The scale goes from left side or zero "0", signifying no pain, to the right side or "10", signifying the worst possible pain. During visit subjects will mark a spot on the line where they feel indicates their current level of pain. A sample VAS is shown in **Figure 1**. Sites will measure from 0 to the mark and record the value in millimeters as the measurement.

FIGURE 1 SAMPLE VISUAL ANALOG SCALE (VAS)*



*** Not to Scale**

12.2 SCHIRMER'S TEST

Bilateral Schirmer's test will be done bilaterally at visits as indicated in **Table 2**. No numbing agents will be used. The investigator pulls the bottom eyelid down and a paper test strip is placed inside at 1/3 distance from the temporal edge of lid margin. The patient is instructed to close the eye(s) and the paper strip is held in place for 5 minutes. The strip is removed, and test results are evaluated.

Evaluation of the Schirmer's test:

1. Normal which is ≥15 mm wetting of the paper after 5 minutes.
2. Mild which is 14-9 mm wetting of the paper after 5 minutes.
3. Moderate which is 8-4 mm wetting of the paper after 5 minutes.
4. Severe which is <4 mm wetting of the paper after 5 minutes

12.3 NON-INVASIVE TEAR BREAK UP TIME (NI-BUT)

A non-invasive way to measure vision fluctuation, analyzing the tear film in its natural state, without disturbing it is NI-BUT. OCULUS Keratograph® is an advanced corneal topographer with a built-in real keratometer and a color

camera that will be used in this study to collect NI-BUT data per the schedule in **Table 2**. The assessment will be performed bilaterally and per the equipment's manual and will be measured and recorded in seconds on the CRFs.

12.4 UNCORRECTED VISUAL ACUITY (UCVA) TEST METHODS

Uncorrected visual acuity (UCVA) at Screening and appropriate scheduled follow-up visits in both eyes per **Table 2** Subjects will remove their glasses or contact lenses. At a distance of 20 feet (6 meters), from the eye chart, the patient will keep both eyes open but cover one eye with the palm of their hand, a piece of paper, or a small paddle. The subject will read aloud the smallest line of letters that they can see on the chart. The Snellen equivalent will be captured on the CRF.

In order to provide standardized and well-controlled assessment of visual acuity, all visual acuity assessments for a subject should be performed consistently (e.g., the same lighting conditions, eye chart, viewing distance, etc.) at each visit.

12.5 SLIT LAMP EXAMINATION

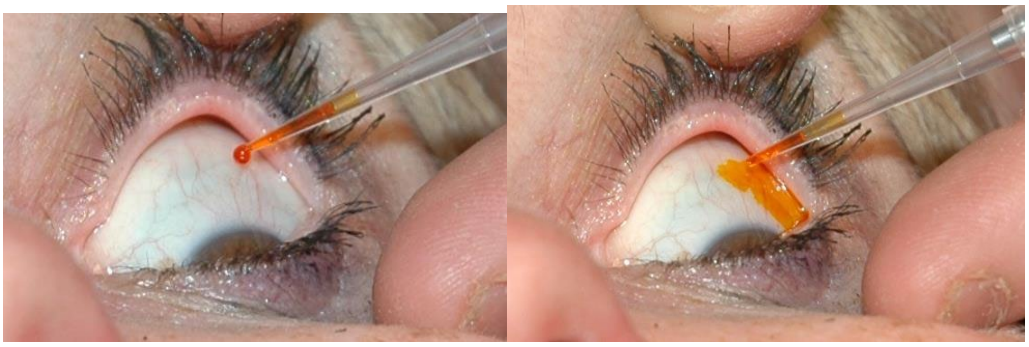
Slit lamp biomicroscopy will be performed bilaterally at all study visits, with assessment of the eyelids, puncta, conjunctiva, cornea, anterior chamber, lens and anterior vitreous. Refer to **Table 2** for the visit schedule.

12.6 CORNEAL FLUORESCEIN STAINING AND GRADING

Refer to **Table 2** for the visit schedule.

Grading of the corneal fluorescein staining in both eyes will be assessed between 2 to 4 minutes following the instillation of 5 µl of 2% sodium fluorescein into the lower conjunctival cul-de-sac of the eye (**Figure 2**). The 5 µl drop of the 2% fluorescein (fluorescein 2 % eye drops, preservative-free solution) will be collected from the container using a micropipette. The National Eye Institute (NEI) scale (**Figure 3**) will be used to assess corneal staining at the slit lamp set at 10X magnification using a broad and diffuse slit lamp beam and a yellow barrier filter to illuminate the entire cornea.

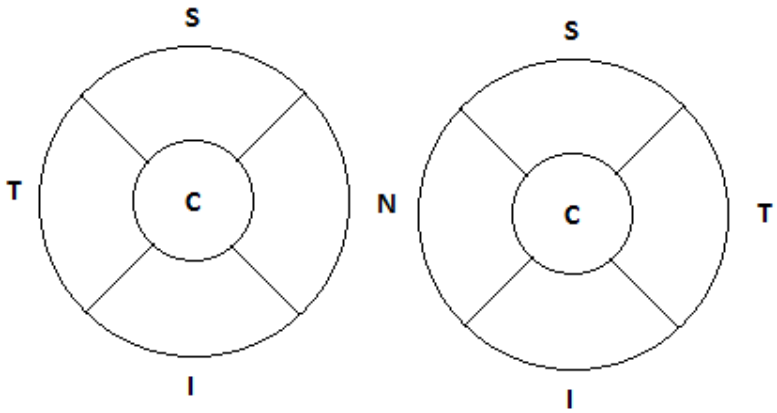
FIGURE 2: CORNEAL FLUORESCEIN STAINING



Corneal staining in both eyes will be graded using the NEI staining grid (**Figure 3**) in which a score of 0 – 3 (0 = normal and 3 = severe) will be assigned to each of the five corneal regions (nasal, central, temporal, inferior, and superior) with a maximum score of 15.

FIGURE 3: NEI STAINING GRID

OD		**OS**
Degree of Staining	**Region**	**Degree of Staining**
0 1 2 3	C- Central	0 1 2 3
0 1 2 3	S- Superior	0 1 2 3
0 1 2 3	T- Temporal	0 1 2 3
0 1 2 3	N- Nasal	0 1 2 3
0 1 2 3	I- Inferior	0 1 2 3
Total: _____		**Total:** _____



Grade 0 = Normal	No staining
Grade 1= Mild	Superficial stippling micropunctate staining
Grade 2= Moderate	Macropunctate staining with some coalescent areas
Grade 3= Severe	Numerous coalescent macropunctate area and/ or patches

(Novack 2017)

12.7 SLIT LAMP PHOTOGRAPHY

Within approximately 30 seconds to 1 minute after the instillation of the fluorescein, the first digital slit lamp corneal photo of the study eye will be taken to document the observed corneal findings. Approximately 3 minutes after instillation of the fluorescein, the second and third photographs will be taken. The digital corneal slit lamp photos of the complete cornea with fluorescein will be taken at 10X magnification using a blue light filter for the main illumination and with extra flashlight, if available. All photos taken must show the entire cornea.

All slit lamp photos must be taken per the schedule in **Table 2**.

The procedures for capturing and exporting slit lamp images of the corneal defect will be detailed in the Imaging Procedures Manual that will be provided to each site.

A Cobalt blue light is used to determine the corneal epithelial defects. Three images per eye are captured and exported from the slit lamp system.

12.8 PATIENT DIARY

At the Baseline visit the site will provide the patient with a Patient Diary to document all investigational product applications (See **Table 2**). A sample of the patient diary is found in **Table 3**. At the Week 1, 2, and 3 visits the site will review the subject's entries in the diary and discuss any missed or inappropriately dispensed applications. Retraining guidance will be provided. At the Week 4 visit (Day 28 ±2 days) the Patient Diary will be collected by the site.

TABLE 3 SAMPLE OBG PED-001 PATIENT DIARY

Day	Date	Application of Study Product (Applied 6 times per day)											
		1		2		3		4		5		6	
		Eye	Time	Eye	Time	Eye	Time	Eye	Time	Eye	Time	Eye	Time
1	__/__/____	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM
2	__/__/____	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM
3	__/__/____	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM
4	__/__/____	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM
5	__/__/____	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM

Day	Date	Application of Study Product											
		1		2		3		4		5		6	
		Eye	Time	Eye	Time	Eye	Time	Eye	Time	Eye	Time	Eye	Time
6	__/__/____	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both	__:__ ☐ AM ☐ PM
7	__/__/____	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM
8	__/__/____	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM
9	__/__/____	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM	☐ Right ☐ Left ☐ Both ☐ NA	__:__ ☐ AM ☐ PM

Completed by Study Coordinator:

Comment on any missed applications above:

_____

Note any new medication(s), date(s) and reason(s):

_____

12.9 INVESTIGATOR GLOBAL EVALUATION OF EFFECTIVENESS

Done per the schedule in **Table 2** and will record the investigator's opinion on the effectiveness of the investigational product in the treatment of a particular subject at study exit by using one of the following descriptions:

- **Very Satisfactory**
- **Satisfactory**
- **Not Very Satisfactory**
- **Unsatisfactory**

13. APPENDIX 2: SPONSOR'S OBLIGATIONS

GENERAL RESPONSIBILITIES OF SPONSORS

Sponsors are responsible for selecting qualified Investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, and ensuring that each local investigator has obtained local Ethics Committee review and approval.

SPECIFIC RESPONSIBILITY OF SPONSORS

1. Selecting Investigators - A Sponsor shall select Investigators qualified by training and experience to investigate the device.
2. Obtaining Agreements - A Sponsor shall obtain from each participating Investigator a signed agreement that includes:
   a) The Investigator's curriculum vitae.
   b) Where applicable, a statement of the Investigator's relevant experience, including the dates, location, extent, and type of experience.
   c) A statement of the Investigator's commitment to:
      (1) Conduct the investigation in accordance with the agreement, the investigational plan, and conditions of approval imposed by the reviewing local Ethics Committee;
      (2) Supervise all testing of the device involving human subjects; and
      (3) Ensure that the requirements for obtaining informed consent are met (21CFR Part 50).

SPONSOR RECORDS

A Sponsor shall maintain the following accurate, complete, and current records relating to an investigation for a period of 3 years after completion of the study:

1. All correspondence with a monitor, an Investigator, a local Ethics Committee, including required reports.
2. Records of shipment. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and serial number.
3. Signed Investigator agreements.
4. Records concerning adverse device effects (whether anticipated or unanticipated) and complaints.

SPONSOR REPORTS

A Sponsor shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects - A Sponsor who conducts an evaluation of an unanticipated adverse device effect shall report the results of such evaluation to the reviewing local Ethics Committee and participating Investigator within 10 working days after the Sponsor first receives notice of the effect.
2. Progress Reports - At regular intervals, and at least yearly, a Sponsor shall provide the site with information to submit progress reports to all reviewing local Ethics Committee.

14. APPENDIX 3: INVESTIGATOR'S AGREEMENT AND OBLIGATIONS

GENERAL RESPONSIBILITIES OF INVESTIGATORS

An Investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable national and local Ethics Committee regulations, for protecting the rights, safety,

and welfare of subjects under the Investigator's care, and for the control of devices under investigation. An Investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS

1. Awaiting approval - An Investigator may determine whether potential subjects would be interested in participating in an investigation but shall not request the written informed consent of any subject to participate and shall not allow any subject to participate before obtaining local Ethics Committee approval.
2. Subject Qualification -The Investigator is responsible for ensuring that all subjects entering the study conform to the patient selection criteria.
3. Compliance - An Investigator shall conduct an investigation in accordance with the signed agreement with the Sponsor, the investigational plan, all applicable ICH GCP regulations, and any conditions of approval imposed by the local Ethics Committee or ICH.

INVESTIGATOR RECORDS

A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation for a period of 3 years after completion of the study:

1. All correspondence with another Investigator, the local Ethics Committee, the Sponsor, a monitor, or other applicable regulatory bodies, including required reports.
2. Records of each subject's case history and exposure to the device. Case histories include the study CRF's/worksheets and supporting data including, for example, signed and dated consent forms and medical records. Such records shall include:
    a) Documents evidencing informed consent.
    b) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
3. The protocol, with documents showing the dates and reasons for each deviation from the protocol.
4. Any other records that local Ethics Committee requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

INVESTIGATOR REPORTS

An Investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects - An Investigator shall submit to the Sponsor and to the reviewing local Ethics Committee a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.
2. Withdrawal of the local Ethics Committee Approval - An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing local Ethics Committee of the Investigator's part of an investigation.
3. Progress - An Investigator shall submit progress reports on the investigation to the Sponsor, the monitor, and the reviewing local Ethics Committee at regular intervals, but in no event less often than yearly.
4. Deviations from the Investigational Plan - An Investigator shall document and report to the Sponsor any deviation from the investigational plan.

5. Informed Consent - If an Investigator enrolls a subject without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing local Ethics Committee within 5 working days after knowledge of this event occurs.
6. Final Report - An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the Sponsor and the reviewing local Ethics Committee.
7. Other - An Investigator shall, upon request by a reviewing local Ethics Committee or national governing body, provide accurate, complete, and current information about any aspect of the investigation.

15. APPENDIX 4: DECLARATION OF HELSINKI

DECLARATION OF HELSINKI

Adopted by the 18th World Medical Association (WMA) General Assembly Helsinki, Finland, June 1964 and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975,
35th WMA General Assembly, Venice, Italy, October 1983,
41st WMA General Assembly, Hong Kong, September 1989,
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, United States of America, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. PREAMBLE

1. The WMA has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

2. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

3. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

B. GENERAL PRINCIPLES

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care."
5. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
6. Medical progress is based on research that ultimately must include studies involving human subjects.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
9. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
10. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
11. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
12. Medical research should be conducted in a manner that minimizes possible harm to the environment.
13. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
14. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
15. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
16. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensure

C. RISKS, BURDENS AND RESULTS

17. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

18. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

19. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

D. VULNERABLE GROUPS AND INDIVIDUALS

20. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

21. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

E. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

22. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
23. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed.

    The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F. RESEARCH ETHICS COMMITTEES

24. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious AEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

G. PRIVACY AND CONFIDENTIALITY

25. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

H. INFORMED CONSENT

26. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
27. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

28. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
29. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
30. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
31. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study

has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

32. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
33. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

I. USE OF PLACEBO

34. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

J. POST-TRIAL PROVISIONS

35. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

K. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

36. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
37. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

L. UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

38. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.