STUDY PROTOCOL

Title: A Randomized Multicenter Double-Masked Placebo-Controlled Parallel Phase 1/2 Study to Determine the Safety and Exploratory Efficacy of Topical Fibrinogen-Depleted Human Platelet Lysate in Patients with Dry Eye Secondary to Graft vs. Host Disease

Protocol Number:	CAM-101-01
Amendment:	NA
Name of Test Drug:	CAM-101
Name of Active Biologic Ingredient:	FD hPL (fibrinogen-depleted human platelet lysate)
Phase of Study:	1/2
Version:	1.4
Date of Approval:	Original July 21, 2017
Study Sponsor:	Cambium Medical Technologies, LLC. 1055 Brookhaven Walk, NE Atlanta, GA 30319-4659
Issue Date:	Original July 21, 2017 Amendment 0.1 Sep 21, 2017 Amendment 0.2 March 21, 2018 Amendment 0.3 July 20, 2018 Amendment 0.4 September 19, 2018

Regulatory Statement

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

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons for whom this information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

Revision History

Version Number	**Version date**	**Summary of Revisions Made**	
		Major	**Administrative**
Version 0.001	09JAN2017	original	Original
Version 0.2	14MAY2017	Names of investigators removed from title page Added study Follow-up period Added drug safety physician Added stopping rules Added primary outcome measures Added exploratory outcome measures Revised primary objective to reflect comparison with placebo Added dynamic allocation to randomization plan Added exclusion criteria per GCP Added blood draw for safety labs at screening	

Version 0.3	07JUNE2017	SAE information added Corrected study flow diagram Changed exclusion #8 to disallow replacement of punctal plugs that fall out Revised record of alcohol, tobacco, and marijuana use	
Version 0.4	14June 2017	Signature page Grammar Treatment emergent adverse events	

Version 0.5	04July 2017	Section 8.1, 12.3.1.1, and Table 3 Treatment emergent adverse events explained Concentration to be used in open label crossover changed to allow flexibility 5 IRBs added Safety labs withdrawn at follow up except in the case of SAE Drop size changed from 50 to 35 µL Section 8.4 Significant improvement in severity defined as >50% improvement on Refresh tears Section 10.6.1 Randomization updated Section 21.1 Updated ocular exam: lissamine green and fluorescein scoring and filter 21.2 Separated ocular discomfort from symptom frequency scales Section 21.8 Instillation techniques updated Section 21.11 Lissamine green staining updated with graphic Section 21.12 Added transport, storage and handling section with figures	

Version 0.6	17July 2017	Rather than say Sponsor will provide sites with all Investigational Product AND study Refresh Plus, re-write to allow option of supplying Refresh Plus 1) either by Sponsor; or 2) from clinical site pharmacy charged against Cambium's site contract and budget Added plasma FSH to Table 8	
Amendment 0.1	September 21, 2017		Consistency: sections 8.1 and 8.4 This special population of 'high responders' will be limited to 12 patients throughout the study Changes highlighted in text
Amendment 0.2	March 21, 2018	Change in exclusion #9 to allow punctal plugs to be replaced if they become dislodged during the study	Administrative changes in SAE reporting to be consistent with Medelis Safety associate

			Administrative changes in exclusion criteria 4 to remove the criterion for destruction of the conjunctival goblet cells or scaring since this is seen in every oGvHD subject

Amendment 0.3	July 20, 2018	Section 7.4 Amend secondary objective to "Change from baseline in lissamine green conjunctival staining on Day 42" Section 8.1 Amend Screening day procedures to stop recreational use of marijuana products. Change to reflect permissible use of marijuana that has been prescribed by a licensed practitioner Section 7.5 Add 3 new exploratory objectives Section 8.1 Eliminate need for urinalysis at screening for safety labs. Eliminate the need for Fasting blood draw safety labs at screening. Add Result by 3rd party- can be used for the trial if they have been conducted within the last 30 days Section 9.1 Eliminate Inclusion #4, need for at least 1 tear osmolarity measurement at screening Section 9.2 Remove Exclusion #16; the need to have HIV, HCV HBV blood tests performed at screening. Allow Viral status to be determined through medical history Section 9.2 Amend exclusion #17 and place responsibility on the investigator to rule out patients who may be abusing alcohol, marijuana or other drugs Section 8.1 Add explanatory language for - "Investigator to administer alcohol screen by questionnaire (appendix 21.6). Drug abuse screen by urine" Section 9.3.1 Amend Stopping rules for SAE that are related to drug and failure of investigator to comply with the protocol	Administrative changes in Style and grammar Abbreviations Definition of brief physical exam Definition of Symptom Severity Explanation of QID dosing Order of ocular examinations Tonometer use for IOP

		Section 10.3 Simplify prohibited medications to include contact lenses Section 10.3 Expand Pain rescue medications to allow medication prescribed by a physician Section 10.4 Remove limitations on consumption of food or food types Section 11.7 Amend language on expiration dating of Investigational product Section 13.7 and 13.7.1 Remove blood chemistry and urinalysis panel Section 12.1.3.2 Relax the timing for first dose Section 12.1.3.3. Reduce the observation period after first dose from 2 h to 30 mins Appendix 21.1 and 21.12 Change the scoring, scale, and graphic for corneal staining with fluorescein Appendix 21.1 and 21.12 Change the scoring and scale for conjunctival staining with lissamine	
Amendment 0.4	September 19, 2018	1 IRB removed 2 IRBs added Remove WCCT and update to Medelis Sec 9.2 Change in exclusion criteria # 2 to allow patients with glaucoma to remain on ocular therapy	

PROTOCOL SIGNATURE PAGE

Title: **A Randomized Multicenter Double-Masked Placebo-Controlled Parallel Phase 1/2 Study to Determine the Safety and Exploratory Efficacy of Topical Fibrinogen-Depleted Human Platelet Lysate in Patients with Dry Eye Secondary to Graft vs. Host Disease**

Protocol Number: **CAM-101-01**

Date of Approval: September 19, 2018

Version: **1.4**

Sponsor's Authorized Representative:		
Terence A. Walts, MBA President and CEO Cambium Medical Technologies, LLC		
Date		19-SEP-2018
Sponsor's Study Director:		
Edmund K. Waller, MD, Ph.D Co-founder, Study Director, Medical and Scientific Advisor Cambium Medical Technologies, LLC		
Date		19-SEP-2018

STUDY CONTACT INFORMATION

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Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
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Drug Safety Physician	Edmund K. Waller, MD, PhD Emory School of Medicine Departments of Medicine, Pathology, and Hematology and Medical Oncology	890 Los Angeles Ave, NE Atlanta, G 30306 **Office:** +1 404-693-7796 **Email:** ewaller@emory.edu

STUDY ADMINISTRATIVE STRUCTURE Clinical Research Organization

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Development of the Protocol and Statistical Analysis Plan Cheryl L. Rowe-Rendleman, Ph.D.

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Independent Institutional Review Boards (IRBs)

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Packaging and Labeling of Investigational Drug

Stemmatters Biotecnologia e Medicina Regenerativa

AVEPARK

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Release Testing

Sterility	Laboratorio Echevarne C/ Reina Victoria, 5 Bjs. 36001 Pontevedra. Spain
Osmolality/Micro-organism Identification	Clinica Laboratorial de Guimarães Rua Nª Srª da Conceição, nº 23. 4800-163 Guimarães. Portugal
Particulate matter	Laboratórios Atral Rua da Estação, 42, Vala do Carregado, 2600-726 Castanheira do Ribatejo Portugal

Manufacturing and Packaging

Dosage Bottle and Cap	Wheaton 1501 North 10th Street Millville, New Jersey, USA 08332-2038
32-pack carton with dividers	Gain How Printing Co., Ltd. No.108-2, Sec. 1, Guangfu Rd. Sanchong Dist., New Taipei City 241 Taiwan
Carton Shipper	FedEx Corp. 9F, No.61, Chung Shan N. Road, Sec. 2, Taipei City 104 Taiwan

3. SYNOPSIS

Name of Company: Cambium Medical Technologies, LLC.	
Name of Study Medication: CAM-101	
Name of Active Ingredient: FD hPL (fibrinogen-depleted human platelet lysate)	
Title of Study: A Randomized Multicenter Double-Masked Placebo-Controlled Parallel Phase 1/2 Study to Determine the Safety and Exploratory Efficacy of Topical Fibrinogen-Depleted Human Platelet Lysate in Patients with Dry Eye Disease Secondary to Graft vs. Host Disease	
Study Center: Up to 6 investigative sites in the U.S.	
Protocol Number: CAM-101-01	
Study Duration: Approximately 6 months	**Study Phase: 1/2**
Objectives: **Primary:** To evaluate the safety and tolerability of two concentrations of CAM-101 (FD hPL 10 vol/vol % and 30 vol/vol %) topical ophthalmic solution in patients with dry eye disease (DED) secondary to graft versus host disease (GvHD) after 6 weeks (42 days) of treatment. **Secondary:** To compare the preliminary efficacy of two concentrations of CAM-101 (FD hPL 10 vol/vol % and 30 vol/vol %) to each other and to a vehicle control in the treatment of patients with DED secondary to GvHD as the result of allogeneic stem cell transplantation.	
Study Patient Population: Approximately 60 patients (~20 in each of 3 treatment groups) are anticipated to complete the core study. To ensure that 60 patients complete the study, up to 72 patients will be enrolled in the core study.	
Study Methodology: This is a Phase 1/2, randomized, double-masked, parallel-group, multi-center clinical trial to evaluate the safety and exploratory efficacy of two concentrations of FD hPL eye drops compared to vehicle control eye drops in adult patients with DED secondary to GvHD. The CAM-101-01 study is a randomized, vehicle-controlled, double-masked study for the first 42 days of dosing followed by an open-label, active only, crossover phase for the second 42 days of dosing. Patients of at least 18 years of age, with DED secondary to GvHD will be randomly assigned (1:1:1) to 1 of 3 groups: FD hPL at either 10 vol/vol% or 30 vol/vol% concentration, or vehicle control composed of PlasmaLyte. Patients will have a 66% chance of being randomized to receive FD hPL test product. Patients will administer 1 drop into both eyes (OU), four (4) times a day (QID) for a period of 42 days. At the end of 42 days, and if there are no drug-related serious adverse events, patients that were randomized to treatment with vehicle will be offered the opportunity to enter the open-label, crossover phase of the study and receive an additional 42 days of treatment with FD hPL test product at the highest concentration tolerated based on overall safety during the first 42 days of dosing.	

Name of Company: Cambium Medical Technologies, LLC.

Name of Study Medication: CAM-101

Name of Active Ingredient: FD hPL (fibrinogen-depleted human platelet lysate)

Stopping Rules: Further administration of the study medication to a patient within a dose group will be terminated under the following circumstances:

1. A patient in a dose group experiences a serious adverse event (SAE) that is possibly drug related
2. A patient withdraws consent to continue in the study

Further administration of the study medication to a dose group will be terminated under the following circumstances:

1. Two or more patients in a dose group experience SAE believed to be related to drug
2. The study is prematurely discontinued by the Sponsor or regulatory authority

Further administration of the study drug products by a study site may be discontinued under the following circumstances:

1. Failure of the Investigator to comply with applicable current regulations and Good Clinical Practice (GCP)
2. Failure of the Investigator to accrue patients into the study at an acceptable rate
3. Failure of the Investigator to comply with the provisions of the protocol

Main Inclusion Criteria: Patients of 18 years of age or older, who have been diagnosed with DED secondary to GvHD following allogeneic hematopoietic stem cell transplantation Schirmer's tear test results with anesthesia of <7 mm/5 min in at least one eye at the screening visit inclusive at the time of signing the Informed Consent Form (ICF).

Study and Reference Drug:

Study Active Biological Ingredient: FD hPL (fibrinogen-depleted human platelet lysate) encompassing a variety of proteins, small molecules, lipids, and electrolytes in a preservative free eye drop.

Reference Drug: PlasmaLyte-A, vehicle control, a preservative-free ophthalmic drop containing only Generally Recognized as Safe (GRAS) excipients.

Dose Administration: Patients will administer a single drop of CAM-101 (FD hPL at either 10 vol/vol% or 30 vol/vol% concentration) or vehicle control into both eyes (OU) four (4) times a day (QID) during waking hours for 42 days. The last drop should be taken at bedtime.

Criteria for Evaluation: The sample sizes for this study were chosen based upon practical considerations. No *a priori* statistical assumptions have been made. Demographic data, including ocular history, will be summarized utilizing descriptive statistics.

Safety Evaluations:

Name of Company: Cambium Medical Technologies, LLC.
Name of Study Medication: CAM-101
Name of Active Ingredient: FD hPL (fibrinogen-depleted human platelet lysate)
Brief physical examinations, vital signs, and a comprehensive ocular examination including an external eye exam, slit-lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, assessments of visual acuity, measurement of intraocular pressure (IOP), and patient comfort and tolerability. **Pharmacokinetic Evaluation** There are no pharmacokinetic studies in this protocol.
Statistical Methodology: **Safety Evaluations:** Brief physical exam, vital signs, AEs, and ocular examinations including IOP, distance visual acuity and patient comfort and tolerability will be summarized using descriptive statistics. Safety and exploratory efficacy data will be collected and reported on all patients in the core study. Safety data will be reported for all patients in the open-label crossover phase following completion of the extension study. **Pharmacokinetic Evaluations:** There are no pharmacokinetic measures in this study.
Date of Final Protocol: July 21, 2017; **Amendment**: September 19, 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Special Term	Explanation
ABI	Active biologic ingredient
AC	Anterior chamber
AE	Adverse event
ARVO	Association for Research in Vision and Ophthalmology
AST	Autologous serum tears
β-hCG	Beta-human chorionic gonadotropin
BCVA	Best-corrected distance visual acuity
BMI	Body mass index
CMO	Contract manufacturing organization
CRA	Clinical research associates
CRO	Clinical research organization
CS	Clinically significant
DED	Dry eye disease
DEWS-II	International Dry Eye Workshop II
eCRF	Electronic case report form
EGF	Epidermal growth factor
ETDRS	Early Treatment Diabetic Retinopathy Study
FD	Fibrinogen-depleted
FD hPL	Fibrinogen-depleted human platelet lysate
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

GCP	Good Clinical Practice
GLP	Good laboratory practice
GMP	Good manufacturing practices

GRAS	Generally recognized as safe
gtt	Gutta (a single drop)
GvHD	Graft versus host disease
HGF	Hepatocyte growth factor
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
HVB	Hepatitis B
HVC	Hepatitis C
IB	Investigator's Brochure
ICAM-1	Intercellular Adhesion Molecule 1
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IFN	Interferon
IND	Investigational New Drug
IOP	Intraocular pressure
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive web-response system

LDPE	Low-density polyethylene (plastic)
LogMar	Log of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mOsm/L	milliosmoles/liter
NCS	Not clinically significant
NZW	New Zealand White rabbits
OD	Oculus dexter (right eye)
OS	Oculus sinister (left eye)
OSDI	Ocular Surface Disease Index
OTC	Over-the-counter
OU	Oculus uterque (both eyes)
phPL	Platelet collections
PI	Principal Investigator
PPS	Per protocol set
PRP	Platelet rich plasma
QC	Quality control
QID	Four times a day
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
Sponsor	Cambium Medical Technologies, LLC
Study Product	All other product dispensed by the Investigator associated with the study—i.e., Refresh Plus® artificial tears.
TBUT	Tear film break-up time

TEAE	Treatment emergent adverse events
TGF-β1	Transforming growth factor beta-1
TID	Three times a day
ULN	Upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
vol/vol %	volume/volume %
VA	Visual acuity
VAS	Visual analogue scale
WHO-DRL	World Health Organization Drug Reference List

6. INTRODUCTION

More than 5 million Americans over the age of 50 suffer from moderate to severe dry eye disease (DED). Ocular graft versus host disease (GvHD) represents a particularly severe form of tear deficiency that develops in 60-90% of patients with chronic GvHD after allogeneic hematopoietic cell transplantation (Nassiri, Eslani et al. 2013).

The definition of DED is evolving. During a presentation at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting in May, 2017, the International Dry Eye Workshop (DEWS-II) characterized DED as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."

Typical symptoms of DED are dryness, burning, and a foreign body sensation that increase as the day goes on. Symptoms may also be described as itchy, scratchy, stingy, or tired eyes. Other symptoms include pain, redness, a pulling sensation, fatigue, light sensitivity, and pressure behind the eye. Both eyes are usually affected.

DED is generally a chronic problem that increases in severity with time. Its prognosis is variable, depending upon the duration of the condition and the severity of the underlying pathology. Chronic DED can lead to micro-abrasions on the surface of the eyes. In advanced cases, the corneal and conjunctival epithelium undergoes pathologic changes, including squamous metaplasia of epithelial cells and loss of conjunctival goblet cells. Some severe cases result in epithelial defects, neovascularization, scarring, corneal ulceration (sterile and infectious), and even corneal perforation.

Patients with severe DED may not respond to conventional treatments, including artificial tears, punctal occlusion, or topical cyclosporine-A (Dastjerdi, Hamrah et al. 2009). In clinical trials of lifitegrast, the treatment effect for corneal staining an objective sign of DED was not significantly different from the vehicle control in 2 of 3 late stage trials and up to 25% of patients experienced side effects with the newer agent (lifitegrast, CDER 2016). Together these data suggest that there is still ample room for innovation in the treatment of DED.

Graft Versus Host Disease

Graft versus host disease is a major systemic condition that occurs after allogeneic hematopoietic stem cell transplantation (HSCT) and is the largest factor in impairing the quality of life of transplant recipients (Quinto, Campos et al. 2008). In GvHD, donor T-cells recognize host tissue as foreign, due to mismatched major and/or minor histocompatibility antigens, leading to inflammatory reactions commonly seen in the skin, liver, gastrointestinal tract, and eye. The ocular manifestations of GvHD include severe DED (Quinto, Campos et al. 2008, Townley, Dana et al. 2011).

Patients with severe DED secondary to GvHD may develop conjunctival scarring, keratinization, cicatrization of the conjunctiva, and neovascularization with significant loss of vision (Nassar, Tabbara et al. 2013). These manifestations can occur in up to half of patients with chronic GvHD (Quinto, Campos et al. 2008). A decrease in tear production is also observed in patients with systemic GvHD (Nassar, Tabbara et al. 2013). Ocular GvHD mimics other immunologically mediated ocular inflammatory diseases. Symptoms can include dry eye, foreign body sensation, redness, and irritation. It can also cause epiphora, photophobia, blurred vision, and severe pain (Nassar, Tabbara et al. 2013). Ocular GvHD occurs in approximately 60-90% of HSCT recipients (Pezzotta, Del Fante et al. 2012). Although systemic immunosuppressive treatment is the primary tool in the management of GvHD and may relieve ocular symptoms, it is often ineffective or not indicated based solely on ocular GvHD symptoms (Nassar, Tabbara et al. 2013).

Current Therapies for DED and GvHD

A variety of topical medications have been employed to treat DED secondary to ocular GvHD, including artificial tears and topical steroids. Restasis® (cyclosporine 0.05% ophthalmic emulsion; Allergan, Irvine, CA) along with Xiidra® (lifitegrast, ophthalmic solution 5%; Shire, Lexington, MA) are the only two prescription medications in the United States indicated primarily for treatment of adult DED. Restasis® is believed to inhibit T-cell activation and IFN-gamma (γ) production. It has also been found to stimulate goblet cell differentiation
(Rafiq, Kasran et al. 1998, Hessen and Akpek 2014). In vitro studies demonstrated that Xiidra® may inhibit T-cell adhesion to ICAM-1 and suppress the secretion of pro-inflammatory cytokines (Paton 2016).

At present, Restasis® is the most common method of dry eye treatment when over-the-counter eye drops are ineffective, notwithstanding the limited efficacy of this product. In a prospective randomized, double-masked controlled clinical trial of Restasis® in 1,200 patients with DED, significantly improved tear production was observed in some patients (15%), but many patients only had partial improvement in symptoms and/or signs, and 17% of patients reported stinging. This latter complication may lead some patients with moderate to severe DED to stop Restasis® treatment prematurely and consequently impede improvement in DED symptoms. Alternative therapies without such complications are therefore needed. Additionally, 1 to 5% of patients develop conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, stinging, and visual disturbances (RESTASIS®, Allergan 1983). The US Food and Drug Administration
(FDA) approved Shire's Xiidra® in July 2016. As a result, clinician and patient acceptance of Xiidra® as an alternative or viable treatment for GvHD DED at present is unknown. Neither Restasis® nor Xiidra® has been approved by the FDA for the treatment of DED secondary to GvHD.

The purpose of this Phase 1/2 study is to compare the safety and tolerability of four times a day (QID) dosing of a non-preserved topical ocular drop formulation of 10 vol/vol % and 30 vol/vol % of FD hPL to vehicle control eye drops in patients with DED secondary to GvHD.

6.1. Previous Clinical and Investigator Initiated Studies

For patients who do not find relief from other modes of therapy, autologous serum tears have been used as an alternative therapy since the mid-1980s. Serum tears are made using coagulated blood samples obtained from individual patients in a doctor's office or lab, mixed with balanced salt solution or commercially available artificial tears, and dispensed by a compounding pharmacy. These preparations approximate some of the constituents of natural tears, including epidermal growth factor (EGF) (Tsubota and Higuchi 2000, Geerling, Maclennan et al. 2004, Soni and Jeng 2016).

The concept of using serum eye drops as a remedy for DED is based on the common belief that nutritive components of serum might substitute for natural tears and improve the health of the ocular surface (Quinto, Campos et al. 2008). Since the initial study in 1984 by Fox (Fox, Chan et al. 1984), a number of clinical trials have been conducted to investigate the efficacy of treatment with serum tears. On average, 77.8% of patients reported some degree of improvement when using autologous serum tears (AST), and these patients overwhelmingly preferred the serum tears to commercially available artificial tears. Likewise, objective signs were reported to be improved as indicated by fluorescein staining scores, rose bengal staining, and tear break up time (TBUT) in 14 patients with severe dry eye associated with GvHD after only 4 weeks of treatment with autologous serum (Ogawa, Okamoto et al. 2003). The efficacy of serum tears is believed to be attributable to the presence of growth factors and other serum constituents including EGF, hepatocyte growth factor (HGF), fibronectin, neurotrophic growth factors, and vitamin A, all of which help to maintain a healthy ocular surface (Tsubota and Higuchi 2000, Geerling, Maclennan et al. 2004, Soni and Jeng 2016).

A report of the tolerability of serum tears in two cases of GvHD with severe dry eyes indicated that treatment with autologous serum eye drops for 10 months duration was safe (Rocha, Pelegrino et al. 2000). A 2007 study assessed the use of allogeneic serum eye drops to treat patients with chronic GvHD-induced severe ocular surface disease (Chiang, Lin et al. 2007). This study concluded that allogeneic serum eye drops may be a good alternative treatment for patients with severe dry eyes caused by GvHD (Chiang, Lin et al. 2007). In fact, serum tears are commonly used by ophthalmologists to treat severe cases of tear deficiency (including those that are unresponsive to commercially available products (Aggarwal et al., 2015).

More recently, platelet enriched plasma has been used to successfully treat patients with dry eye as well as other ocular surface disorders (Alio, Colecha et al. 2007, Alio, Rodriguez et al. 2015, Espandar 2016). Pezzotta et al. found that autologous platelet-rich plasma lysate improved signs and symptoms in patients with GvHD that had not responded to conventional therapy (Pezzotta, Del Fante et al. 2012), while Alio et al. reported improvement in signs and symptoms of DED with topical platelet-rich plasma (Alio, Colecha et al. 2007, Alio, Rodriguez et al. 2015). Topical autologous platelet-rich plasma has also been shown to be safe and effective for the treatment of acute cornea chemical injuries (Panda, Jain et al. 2012) and non-healing sterile corneal ulcers (Alio, Abad et al. 2007).

Limitations such as the need for periodic blood draws, the lack of standardization in the preparation of AST and platelet-enriched plasma tears, the unknown shelf life of AST preparations, the use of non-preserved

multi-dose packaging and the practical difficulties patients face in storing these products frozen or refrigerated have hindered their widespread use for treating GvHD and other forms of severe tear deficiency.

To address these shortcomings, Cambium Medical Technologies, LLC has developed a proprietary method of standardizing and manufacturing a fibrinogen-depleted standardized platelet lysate using pooled human platelet lysates (phPL) collected from qualified healthy donors (CAM-101). Because Cambium's proprietary manufacturing process depletes pooled human platelet lysates of fibrinogen (the key clotting protein in platelets), the remaining product contains enriched levels of several key nutritive and regenerative components than are normally found in non-standardized AST as well as healthy tear film. Given the multi-factorial nature of DED, the enriched levels of numerous key nutritive components in CAM-101 may well prove to be superior to artificial tears and certain single active ingredient products which treat only one cause or contributor of dry eye (e.g., inflammation) and other forms of tear deficiency.

6.2. Preclinical Study Findings

Two nonclinical toxicology studies were conducted with CAM-101 (3%-50% FD hPL) in rabbits, and no ocular toxicity, irritation, or systemic toxicity was found. No other preclinical studies have been conducted with CAM-101.

6.2.1 Pharmacology

There have been no pharmacology studies in animals.

6.2.2 Pharmacokinetics and Drug Metabolism in Animals

There have been no pharmacokinetics or metabolism studies in animals.

6.2.3 Tolerability, Safety, and Toxicology

21-Day Ocular Irritation Study in New Zealand White Rabbits (Study No. 13-03098-N1)

In the non-GLP toxicology study (Study No. 13-030398-N1), 8 week-old male rabbits (n = 8) were instilled (30 µL) with either the test article (50% FD hPL diluted in PlasmaLyte-A) in the left eye or the vehicle (PlasmaLyte-A) in the right eye three times a day (TID) between 8 am and 6 pm for 21 days. Clinical observations, body weight changes, and ocular examination (slit lamp) were examined to evaluate any test-article-related ocular irritation and systemic toxicity.

There were no test article-related findings following topical administration (30 µL) of FD hPL (50% dilution) TID for 21 days in New Zealand White (NZW) rabbits.

In conclusion, FD hPL at 50% concentration did not cause any ocular toxicity, irritation (slit lamp examination), or systemic toxicity (body weight) in NZW rabbits after 21 days of TID treatment.

Toxicity studies

42-Day Ocular Topical Repeat Dose Toxicity Study in Dutch Belted Rabbits (Study No. 1401876-G1)

In the GLP toxicology study (Study No. 14-01876-G1), pigmented Dutch Belted rabbits were pre-screened for ocular abnormalities, and only animals with a normal ocular exam were used for the study. Prior to study initiation, ocular examinations were performed oculus uterque (OU, in both eyes) in all animals, and body weights were measured. In addition, venous blood samples were collected for baseline clinical chemistry and hematology analysis.

Animals were randomized into 4 groups of 8 animals each (4 males and 4 females). Group 1 was treated with vehicle (PlasmaLyte-A); Group 2 with FD hPL 3 vol/vol%; Group 3, with FD hPL 10 vol/vol%; and Group 4 with FD hPL 30 vol/vol%. Rabbits were dosed in both eyes with 30 µL vehicle or the appropriate test article TID. Dose administrations were at least 3 hours apart. The first day of drop administration was considered Study Day 1.

Throughout the study, on a weekly basis, body weight measurements, food consumption calculations, and ocular examinations were carried out. At the time of sacrifice, body weights were recorded and ocular examinations were performed. In addition, on Day 8 of the study and on the day of sacrifice, blood samples were collected for clinical chemistry and hematological analysis. Following gross necropsy, the eyes were enucleated and processed for histopathological analysis.

No test article-related abnormal clinical observations were recorded at any time during the study. Body weights, food consumption, and ocular examinations in treatment groups were similar to animals dosed with vehicle. Histopathological analysis of the eyes revealed some minor and focal mononuclear cell infiltration in conjunctiva. However, the incidence of the noted infiltration was similar across all groups and not related to the test article.

In conclusion, the topical administration of FD hPL in concentrations up to 30 vol/vol% did not reveal any indication of ocular or systemic toxicity nor were changes recorded in body weight, food consumption, or blood chemistry in Dutch Belted rabbits when compared to the vehicle-treated animals.

Genotoxicity Studies

There were no genotoxicity studies conducted.

Reproductive Toxicity Studies

There were no reproductive toxicity studies conducted.

Dermal, Ocular Irritancy, and Delayed Dermal Sensitization Studies

There were no dermal or delayed sensitization toxicity studies. There was no ocular irritancy as indicated by Draize McDonald-Shadduck and Posterior Segment analysis scores.

7 STUDY OBJECTIVES AND PURPOSE

7.1 Primary objective

The primary objective of this study is to compare the safety and tolerability of two concentrations of CAM-101 (10 vol/vol % and 30 vol/vol % FD hPL topical ophthalmic solution) to a vehicle control eye drop in the treatment of patients with DED secondary to GvHD as the result of allogeneic stem cell transplantation after 42 days of QID dosing.

7.2 Secondary objectives

The secondary objective is to compare the preliminary efficacy of two concentrations of FD hPL (10 vol/vol % and 30 vol/vol %) to each other and to a vehicle control in the treatment of patients with DED secondary to GvHD as the result of allogeneic stem cell transplantation as measured by change in corneal staining, ocular surface disease index (OSDI) and ocular discomfort using the 100 point visual analogue scale (VAS) scores.

7.3. Primary Outcome Measures

The primary outcome measures are:

- Percentage of patients in each dose group with ocular adverse events at Day 42
- Percentage of patients in each dose group with systemic adverse event at Day 42
- The number of patients in each dose group that show a change from Normal to Abnormal with clinical significance in any ocular examination assessment at Day 42

7.4. Secondary Outcome Measures

The secondary outcome measures are:

- Change from baseline in fluorescein corneal staining on Day 42
- Change from baseline in lissamine green conjunctival staining on Day 42
- Change from baseline in ocular discomfort score as measured with VAS on Day 42
- Change from baseline in OSDI score on Day 42

7.5. Exploratory Outcome Measures

The exploratory outcome measures are:

- Change from baseline in the tear osmolarity at day 42
- Change from baseline in Schirmer's test at day 42
- Change in investigators global evaluation after 42 days of dosing

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design

This will be a Phase 1/2, multiple-dose study of FD hPL in adult male and female patients with DED as a result of GvHD following allogeneic bone marrow transplantation. The overall design is a vehicle-controlled, randomized, double-masked, parallel-group comparison study.

After Informed Consent is obtained, a medical history will be recorded, and potential patients will be examined and screened for eligibility. The study consists of a Screening Period (Day –30 to Day –14) to confirm compliance with all inclusion and exclusion criteria. After the initial screening period, there will be a 2-week vehicle Run-in period (Day –14 to Day 0) with patients allowed to take only site- or Sponsor-supplied preservative-free artificial tears (Refresh Plus®, carboxymethycellulose, 0.5%; Allergan, Irvine, CA) as needed. Refresh Plus® is the only artificial tear product allowed during the study. The use of Restasis® and/or Xiidra®, if prescribed for DED, may be continued during the Run-in at the pre-study regimen if subjects are already taking these medications. The use of punctal plugs and certain other medications may be continued during the Run-in at the pre-study regimen if already on these treatments. Other types of DED remedies (e.g. autologous serum, platelet rich plasma [PRP] serum) are not allowed during the study. Patients will record the frequency of their use of artificial tears during the Runin.

At the end of the Run-in period, patients will be evaluated by "Symptom Severity" (a composite of OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, and frequency of use for artificial tears OU) and subsequently randomized by interactive web response system (IWRS) to either active or vehicle control treatment. Dynamic allocation will be used to randomize the patients in each site on the basis of the mean "Symptom Severity" OU. In addition, special populations of highly responsive patients who experienced a significant improvement in "Symptom Severity" defined subjectively by the Investigator as having greater than 50% improvement in the composite of Symptom Severity scores (e.g. an improvement in 3 of 5 components: OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, frequency of use for artificial tears OU, and overall clinical impression) at the baseline visit relative to screening may be enrolled directly into the 30 vol/vol % FD hPL dose group and followed for 42 days for safety analysis. A maximum of 12 patients throughout the study and across all sites shall be enrolled in this way. All others will allocated dynamically by IWRS according to a predefined calculation of "Symptom Severity" at the end of the Run-in period. While efficacy data will be collected and reported for the overall study, the efficacy data from these highly responsive patients will not be included in the preliminary efficacy analysis derived from the core study.

Starting at Visit 1 (Day 1), all randomized patients will receive their baseline assessments and will be treated for 6 weeks (Day 1 to Day 42). Both eyes will be evaluated. Patients in all three dose groups will self-administer a single drop of CAM-101 or vehicle control in both eyes QID (see **Section 8.2**). At a minimum of 30 minutes after instillation of the study medication, the ocular surface will be examined by slit lamp. Patients will be expected to return for two additional study visits at Day 21 ± 3 (Visit 2) and Day 42 ± 3 (Visit 3) and a single Follow-up visit within 7 days of the last dose at Visit 4 (Days 46-52; **Figure 1**).

Patients will report their continued use of Refresh Plus artificial tears as well as other concomitant therapies at both their 21- and 42-Day study visits.

Up to 72 patients may be enrolled in this study to ensure that a net 60 patients complete the full 42-Day study, with 40 net patients receiving CAM-101 test product (20 net patients per concentration level), and 20 net patients receiving vehicle control. All patients except for the special population of highly responsive patients identified after Run-in, will be randomly allocated (1:1:1) on Day 1 to one of three treatment arms: FD hPL 10 vol/vol%, FD hPL 30 vol/vol% concentration, or vehicle control. Patients will have a 66% chance of being randomized to receive FD hPL test product during the core 42-day study. Highly responsive patients will be directly enrolled into the 30 vol/vol% cohort.

Figure 1: Schematic of Overall Study Design

Screening	**Vehicle Run-In**	**Dosing and Evaluation** CAM (10 vol/vol% or 30 vol/vol%) or vehicle	**Follow-up Visit**	**Vehicle Group Crossover** CAM (30 vol/vol%)
(up to 14 days) **Days –30 to –14**	(2 weeks) **Day –14 to 0**	(42 days) **Days 1 to 42**	**Days 46 to 52**	(42 days) **Days 46 to 93**

For this study, surveillance of adverse events (AE) will begin from the day the patient signs the informed consent form (ICF) until the end of the treatment period (Day 42) or 30 days after the last dose of investigational product, whichever occurs last. Treatment emergent adverse events (TEAE) will be recorded from the day of the first dose. The reporting of serious AEs (SAE) will follow the same course. Any events that occur before the signing of the ICF will be recorded as medical history.

The study flow charts (**Table 3, Table 4,** and **Table 5**) provide the timing of procedures.

Screening Period (Day –30 to Day –14)

Table 3 describes the events during the Screening, Run-in, and Day 1 dosing and evaluation periods.

Each eligible patient will sign an ICF prior to any study related procedures being performed. Ocular and medical histories will be obtained and a brief physical examination will be performed. A comprehensive ocular examination (**Appendix 21.1**) with fluorescein and lissamine green application to assess the ocular surface will be completed.

The results of non fasting hematology testing that has been conducted in the oncology setting by a third party may be permitted in the trial provided the patient gives consent. The results of these tests are not required to begin the Run in on Day -14.

A medical history indicating no detectable antigens to human immunodeficiency virus (HIV) and Hepatitis (HBV and HCV) within the past 12 months prior to screening is sufficient. In the absence of these,

additional blood work will be performed to assess the presence of antigens to human immunodeficiency virus (HIV) and Hepatitis (HVB and HVC). A questionnaire for substance and alcohol abuse will be done. An evaluation of body weight and height (parameters to be used to calculate a body mass index [BMI]) will be measured. Vital signs (i.e., heart rate, blood pressure, respiratory rate, and body temperature) will be measured.

Female patients must be either surgically sterile, without menses for 12 months (365 days) or have a negative urine pregnancy test for beta-human chorionic gonadotropin (β-hCG).
Pregnancy status will be evaluated at screening and study exit. Concomitant medications will be recorded and the patient will be informed of the necessity to stop smoking tobacco and recreational use of marijuana products and to wash out of all prohibited medications. It is permissible to continue the use of marijuana that has been prescribed practitioner for a medical condition.

Vehicle Run-in (Secondary Screening) Period (Day –14 to Day 0)

Table 3 describes the events during the Run-in period.

Patients who meet eligibility criteria will be given a sufficient supply of artificial tears (Refresh Plus) to be self-administered as often as needed during the 2-week Run-in period. The artificial tears along with continued use of punctal plugs, Restasis® or Xiidra® and other concomitant therapies that have been prescribed by a physician and pre-approved by the Principal Investigator will be allowed during this period. If a plug is lost during the study, the instance must be recorded in the eCRF, and the plug may be replaced.

All concomitant medications must be administered at the pre-study dose and regimen. No new prescription or over-the-counter (OTC) medications except for provided preservative-free artificial tears (Refresh Plus®) are allowed during the Run-in period. The frequency of artificial tear use will be reported and recorded in the patient diary during the Run-in. Symptom severity scores (OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, frequency of use for artificial tears OU, and overall clinical impression) will be assessed within 24 hours of the end of the Run-in. Scores must be recorded on the source document and entered into the electronic case report form (eCRF) before randomization by IWRS can occur. The mean composite "Symptom Severity" OU will be calculated electronically for all patients. The score will be used for randomization for all patients except the special population of high responders. The clinic staff will arrange for admission to the study on the morning of Day 1. Patients will be instructed not to administer any artificial tear, less than 1 hour prior to the visit on Day 1**.**

Predose Admission Period (Day 1, predose)

Table 3 describes the events during the predose period on Day 1.

For convenience, the assessments of Day 0 and Day 1 (predose) can be combined. The Investigator will review the Baseline inclusion and exclusion criteria to confirm eligibility. Any medical or ocular changes since the start of the Run-in period will be recorded on the source document and entered into the electronic case report form (eCRF) comments page. Adverse events will be recorded as observed. The frequency of

artificial tear use will be reviewed with the patient if more than 24 hours have elapsed since the end on the Run-in period. Evaluation of the ocular safety will be performed including best-corrected distance visual acuity (BCVA), slitlamp examination, intraocular pressure (IOP) measurement, and inspection for ocular signs and symptoms of DED (TBUT, corneal fluorescein stain, and conjunctival lissamine green stain, and Schirmer test with anesthesia). Each patient will undergo vital signs determination 30±10 minutes before dose. Concomitant medications will continue to be assessed. Randomization to treatment group will be conducted once eligibility is confirmed at the Baseline visit. The unmasked pharmacist will distribute the kits to each eligible patient according to the interactive web-response system (IWRS). Randomization will be performed by assigning each eligible patient an Investigational Product kit that corresponds to a list generated by the IWRS. Each randomized patient will receive a supply of Investigational Product sufficient for 21 days.

Before the patient administers the first dose, the clinic staff will remind patients about the proper use of the diary and instruct them on appropriate eye drop dosing technique and storage (see **Appendix 21.8** for proper instillation of eye drop).

Dosing and Evaluation Period (Day 1 dose)

Table 3 describes the events during the Day 1 dosing period.

Patients will be instructed to administer one drop of Investigational Product four times daily OU.

The first dose will be administered OU by the patient. (**Table 3**). The time of the first study drug administration for each patient is considered "Time Zero" and shall be noted on the source document and recorded in the electronic case report form (eCRF). The patient shall record the time in the diary. Clinic staff will review the patient diary and advise the patient of the frequency and approximate time for the next 3 doses.

Patients will receive their first dose of study medication at the study site. The clinic staff will provide guidance to each patient as to the appropriate times for dosing the study medications. The next doses are to be administered at a frequency of four (4) times a day during waking hours every day for 42 consecutive days. The last dose of each day should be administered just before bedtime. Patients will be advised to take the drops at the same time every day.

Dosing and Evaluation Period (Day 1 post dose)

Table 3 describes the events during the Day 1 post dose and evaluation period.

Patients will be instructed not to use artificial tears or other concomitant drugs within 6030 minutes (0.5 hours) of instilling investigational drugs. The use of artificial tears and investigational drugs shall be reported and recorded at each study visit.

After the administration of the first dose, patients will remain in the clinic for observation for a minimum of 30 minutes. The final assessment of the day will be a slit lamp examination, which shall include observation of the ocular surface for symptoms of irritation. After the observations and all assessments have been completed, the patient can then be ***discharged from the study unit*** unless they have ongoing, clinically significant AEs. If there are ongoing clinically significant AEs, the Investigator may retain the patient at the site and conduct necessary evaluations. The Investigator may exercise discretion to perform any additional assessments if needed. Additional assessments shall be documented on the source document and recorded in the eCRF.

Prior to discharge, the clinic staff will arrange for the patient to return for the next study visit. Patients will also be instructed to not use either study eye drops or artificial tears within 1 hour prior to each study visit.

Visits 2 and 3 (Days 21 ± 3 and 42 ± 3)

Patients will dose themselves at home with the first daily dose of the morning and bring their diaries as well as the used and unused bottles of CAM-101 Investigational Product to the clinic for collection. The bottles should be placed into their 32-pack cartons before returning them (**Table 4**) on Visit 2 (Day 21 ± 3) and Visit 3 (Day 42 ± 3). The patient should be reminded to take the morning dose of investigational product at least 1 hour before the clinic visit. If this is not possible, then the drop should be avoided until after the clinic visit. At the clinic, the bottles and investigational kits will be collected and the diaries reviewed. All returned product will be used by the Sponsor to help facilitate product accountability and compliance measures per patient and for the study in total. The patient will be reminded to not discuss the appearance of the investigational product with any of the study staff except for the unmasked pharmacist.

The Investigator will assess AEs as described in **Section 14.1**. The patient will be asked to estimate the frequency of use of artificial tears and the Investigator will record the responses at each patient's 21 and 42-day visit. The clinic staff will list concomitant medication usage. Ocular safety assessments will be performed at all visits. An unmasked pharmacist will dispense a new 21-day supply of Investigational Product and artificial tears. After the assessments have been completed, the patient will then be ***discharged from the study unit*** unless there are ongoing, clinically significant AEs. If there are ongoing clinically significant AEs, the Investigator may retain the patient at the site. The Investigator may exercise discretion to perform any additional assessments if needed. Additional assessments shall be recorded in the eCRF.

Prior to discharge, the clinic staff will arrange for the patient to return for the next study visit Patients will also be instructed to not use either study eye drops or artificial tears 1 hour or less prior to each study visit.

On the final dosing day, Visit 3 (Day 42 ± 3), clinic staff will instruct the patient to return for the Follow-up visit.

Visit 4 Study Exit /Follow-up Visit (Day 49 ± 3)

A Follow-up visit is scheduled at Day 49 ± 3. All patients will have an ocular examination, a brief physical examination, and assessment of vital signs (**Table 5**). Blood draws and urinalysis samples for safety will be

required for any patient that experienced a serious adverse event during the study. Approved concomitant medications will also be recorded. Urine will be collected to determine pregnancy for all females of childbearing capacity if there is an early termination prior to Day 42.

After the Follow-up visit and in the absence of any drug-related SAEs during the study, patients who had been assigned to the vehicle treatment group will be offered the opportunity to receive treatment with active test product (FD hPL) at a concentration commensurate with the highest safety profile observed during the first 42 days of dosing. If safety, as measured by the rate of AEs, was equivalent in all groups than 30% FD hPL will be used. All other patients will be ***discharged from the study*** on Day 49 ± 3 provided there are no ongoing clinical or laboratory AEs present. Otherwise, if AEs are present, the Investigator shall continue to Follow-up with the patient until resolution or stabilization of the AE has occurred.

Patients who are eligible to crossover from the vehicle control group to open-label treatment with active test product will be given a new 21-day supply of Investigational Product and artificial tears during the Follow-up visit. Prior to discharge, the clinic staff will arrange for the patient to return for the next study visit at 21 days post dose (Day 70 ± 3). During study visits patients will be instructed to not use the study eye drops or artificial tears within 1 hour prior to their study visit.

Visits 5 and 6 Patient Crossover from Vehicle to Open-label Treatment Group Visit (Day 50 to Day 93)

Patients in the open-label crossover group will be followed for an additional 42 days using the same schedule of dosing and study visits as patients originally treated with test product (**Table 4**). Study visits will occur at Visit 5 (Day 70 ± 3) and Visit 6 (Day 91 ± 2). Safety and exploratory efficacy data will be gathered for safety analysis but these crossover study results may not be included in the secondary efficacy analysis. At the final visit, Visit 6 (Day 91 ± 2), clinic staff will collect the bottles and investigational kits. All returned product will be used by the Sponsor to help facilitate product accountability and compliance measures per patient and for the study in total.

All patients will be ***discharged from the study*** on Day 91 ± 2 provided there are no ongoing clinical or laboratory AEs present.

Early Termination

For patients who terminate early, all scheduled assessments listed for Day 42 should be attempted. In addition, all procedures listed for Day 49 should be completed, if possible. Discharge from the study unit and/or discontinuation from the study will be decided after consultation with the Investigator and Sponsor (Cambium Medical Technologies, LLC).

Table 3: Study Flow Chart for Screening, Predose, and Day 1 Periods

Visit number		**Screening and Run-in**		**Dosing and Evaluation**		
Day (Time)		Day –30 to Day –14	Day –14 to Day 0	Day 1 (Predose)	Day 1 (Dose)	Day 1 (Post dose)
Informed consent		X				
Eligibility criteria		X		X		
Demographics		X				
Medical/surgical/ocular history[1]		X		X		
Body weight and height[2]		X				
Vital signs (body temperature, heart rate, blood pressure, respiratory rate)		X		X[3]		
Review of prior and concomitant medications		X[4]		X[4]		
Physical examination		X[5]		X[5]		
Ocular Exam	Frequency of artificial tear use		X[6]	X		
	Visual acuity (bestcorrected distance visual acuity by Early Treatment Diabetic Retinopathy Study [ETDRS] protocol)	X		X		
	External eye exam/ (eye color)	X				
	Ocular Discomfort (VAS)	X	X[6]			
	OSDI	X	X[6]			
	Symptom frequency rating (VAS)	X	X[6]			
	Tear osmolarity	X		X		
	Slit lamp biomicroscopic exam[7]	X		X		X
	Tear film break up time (TBUT)[8]	X		X		
	Corneal fluorescein stain	X		X		
	Conjunctival lissamine green stain	X		X		
	Schirmer test with anesthesia	X		X		
	IOP	X[9]		X[9]		
	Dilated fundus exam	X[10]				
	Investigator's global evaluation					X
Urine Pregnancy test (females of childbearing capacity only)		X[11]		X[11]		

Plasma FSH	X				
Alcohol and drug abuse questionnaire	X12				
Safety laboratory: 13	X13				
Confirm medical history no HIV, HCV, HBV past 12 mos	X				
Randomization			X		
Dispense new artificial tears		X14		X	
Dispense Investigative Product				X	
Instill Investigative Product				X15	
Adverse event surveillance	X16		X	X16	X
Diary recording and review17		X		X	

Table 4 Cont'd

1. The ocular history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures; **Section 13.2**).
2. BMI to be calculated from weight and height.
3. Baseline vital signs on Day 1 to be completed at least 30 ± 10 mins before dose on Day 1.
4. Review of concomitant medications and confirm that prohibited medications have been discontinued.
5. Brief physical examination comprised of appearance, mood, and affect.
6. Baseline ocular examinations be conducted within 24 hr. of the end of the run-in period (Day 0) and used to calculate Symptom Severity before randomization on Day 1. These assessments on Day 0 may be conducted on Day 1 (predose) provided they are conducted within 24 hours of the end of the run-in period.
7. Slit lamp examination at Screening comprised of eyelid margins and lashes, tear film and function, conjunctiva, sclera, cornea, and assessment of central and peripheral anterior chamber (anterior chamber depth, iris, lens, anterior vitreous for cells and flare. All other slit lamp examinations on Day 1 are for ocular surface: conjunctiva, sclera, cornea
8. Patient must refrain from using any tear supplements within 1 hour of the test.
9. IOP must be measured after all assessments of the ocular surface and cornea are completed.
10. Use a mydriatic agent 30 minutes prior to assessment with indirect ophthalmoscopy.
11. Pregnancy tests for females of childbearing capacity include: urine pregnancy tests at screening and before administration of the first dose.
12. Investigator to administer alcohol screen by questionnaire (**appendix 21.6**). A medical history indicating that this has been conducted within 12 months shall be sufficient.
13. Non-fasted safety labs that have been conducted in the oncology setting by a third party may be permitted in the trial provided the patient gives consent. These tests are not required for admission to the study—but will be used in the event of an SAE
14. Dispense artificial tears on Day –14. Staff will instruct patients on proper dosing technique.
15. On Day 1 patients will be instructed on proper techniques for drug instillation into the eyes. Clinic staff will also provide guidance on how to dose. The first dose will be instilled in the clinic under supervision and the second-fourth dose shall be dosed at home. All doses should be recorded in the patient diary.
16. Adverse events shall be recorded starting at signing of ICF. Treatment-emergent adverse events shall be indicated in study reports after the first dose of study medication.
17. Clinic staff will review the appropriate way to complete the patient diary with each patient.

Table 4: Study Flow Chart for Day 21 ± 3 to Day 42 ± 3 and Crossover

Study Phase		**Dosing and Evaluation**	
Visit number		2	3
Study Day		21 ± 3	42 ± 3
Study Phase		**Open-label Crossover**	
Visit number		5	6
Study Day		70 ± 3	91 ± 2
Instill Investigational Product (IP)[1]		X	X
Vital signs (body temperature, heart rate, blood pressure, respiratory rate)[2]		X	X
Review concomitant medications		X	X
Physical examination[3]		X	X
Ocular examination[4]	Frequency of artificial tear and IP use	X	X
	Visual acuity (best-corrected distance visual acuity using the Early Treatment Diabetic Retinopathy Study [ETDRS] protocol)	X	X
	External eye exam (ocular signs and symptoms)	X	X
	Ocular Discomfort (VAS)	X	X
	OSDI	X	X
	Symptom frequency rating (VAS)	X	X
	Tear osmolarity[5]	X	X
	Slit lamp biomicroscopic exam[6]	X	X
	Tear break up time (TBUT)	X	X
	Corneal fluorescein stain	X	X
	Conjunctival lissamine green stain	X	X
	Schirmer test with anesthesia	X	X
	IOP[7]	X	X
	Dilated fundus exam[8]		X
	Investigators global evaluation	X	X
Pregnancy test (females of childbearing capacity only)[9]			X
Treatment-emergent adverse event surveillance		X	X
Diary review[10]		X	X
Dispense Investigational Product		X	
Dispense artificial tears		X	
Collect Investigational Product[11]		X	X

1. Patients will be instructed to administer the Investigational Product at least 1 hour prior to clinic visit and record the time in the diary. Patients should not take any drops including artificial tear, less than 1 hour prior to the clinic visit.
2. The time that the Vital signs are completed relative to dose shall be recorded.
3. Brief physical examination comprised of appearance, mood, and affect.
4. All ocular examinations to occur in the order written.
5. Patient must refrain from using any tear supplements within 2 hours of the tear osmolarity test.
6. Slit lamp examination comprised of eyelids, iris, lens, vitreous, cells, and flare.
7. IOP must be measured after all assessments of the ocular surface and cornea are completed.
8. Use a mydriatic agent 30 minutes prior to assessment with indirect ophthalmoscopy.
9. Pregnancy tests for females of childbearing capacity include: urine pregnancy test at Visits 3.

10. Clinic staff will review the appropriate way to complete the patient diary with each patient. A new diary card will be provided at Visits 2 and 3.
11. New Investigational Product shall be distributed on Day 21 in the prospective study. Used Investigational product will be collected during the visit on Days 21 and 42. During the open label crossover study, new investigational product will be distributed at Follow-up and on Day 70. Used Investigational Product will be collected on Days 70 and 91.

Table 5: Study Flow Chart for Day 49 ± 3

Study Phase		**Follow-up or Early Termination[1]**
Visit number		**4**
Study Day		**49 ± 3**
Time after administration		
	Vital signs (body temperature, heart rate, blood pressure, respiratory rate)	X
	Review concomitant medications	X
	Physical examination[2]	X
Ocular examination	Visual acuity (best-corrected distance visual acuity using ETDRS protocol)	X
	External eye exam (ocular signs and symptoms)	X
	Slit lamp biomicroscopic exam[3]	X
Pregnancy test (females of childbearing capacity only; urine)[4]		X
Safety laboratory[5]		X
Treatment-emergent adverse event surveillance		X
Collection of diary		X
Dispense investigational product[6]		X

1. All Day 49 procedures will also be completed for any patients who terminate early.
2. Brief physical examination comprised of appearance, mood, and affect.
3. Slit lamp examination at Day 49 comprised of eyelids, iris, lens, anterior vitreous, cells and flare, cornea.
4. Urine analysis for pregnancy is only required for women of childbearing age if there is an early termination prior to Day 42.
5. Only patients who experience SAEs during the study must also receive a safety blood and urine test at Follow-up.
6. Patients who were assigned to vehicle for the first 42 Days and are eligible to enter the open-label crossover study will be given a 21-day supply of active Investigational Product.

8.2 Treatment Assignment

Table 6 describes the proposed parallel treatments. Three dose groups have been planned: Group 1 (CAM-101; 10 v/v % FD hPL), Group 2 (CAM-101; 30 v/v % FD hPL), and Group 3 (vehicle control; **Table 6**). The duration of the study will be approximately 77 days for patients in Groups 1 and 2 and approximately 126 days for patients in Group 3.

Table 6: Summary of Dosage Groups

Proposed Period[1]	**QID Dose**	
	Dose group (n = 20)[2]	**Treatment**
Week 1-2	All eligible	none
Week 2-4	All eligible	Refresh Plus
Week 4-10	1, 2, 3	CAM-101 (10 vol/vol% FD hPL) CAM-101 (30 vol/vol% FD hPL) Vehicle (PlasmaLyte-A)
Week 11	1, 2, 3	none
Week 12-18	3[3]	CAM-101 (FD hPL dose to be determined based on safety of dosing in weeks 4-10)

[1]The study schedule will be adjusted based on completion of enrollment.
[2]If a patient discontinues prematurely, the site, and Sponsor will discuss potential replacement on a case-by-case basis. [3]After the Follow-up visit, patients who had been assigned to the vehicle control treatment with PlasmaLyte-A (Group 3) will be offered the opportunity to receive treatment with active test product CAM-101 (FD hPL) at 10% or 30% vol/vol. The drug will be administered in an open-label format and the concentration chosen will be commensurate with the highest safety profile as determined by dosing in Weeks 4-10. If safety as measured by the rate of AEs was equivalent in all groups then 30% FD hPL will be used. All others will be dismissed from the study. The final number in this crossover group will not exceed twenty, the number in the original vehicle control group. [4]All percent concentrations of CAM-101 are vol/vol.

8.3 Rationale for Dose Selection

Protocols reported for the preparation and usage of autologous serum for DED as well as numerous other ocular surface diseases and conditions vary considerably as to recommended daily dosage (range 2-10 doses/day). Many variables can impact the optimal daily dosage of a drug product. Regarding serum drops one key variable is the concentration of active ingredient in the drug product. With respect to autologous serum, while concentrations vary considerably, the most common and preferred concentration has been 20% vol/vol active solution (Mangan and Lehman 2012, Brennan 2016). This has to do in part with the concentration level of transforming growth factor β1 (TGF-β1) in blood serum. TGF-β1 is believed to inhibit epithelial cell proliferation in a dose-dependent manner (Imanishi, Kamiyama et al. 2000). In serum, the concentration of TGF-β1 has been found to

be five times that of tears. A 20% vol/vol solution of serum keeps TGF- β1 levels at or near physiological levels for tears. Given that up to 10 doses/day have been recommended for AST, the dilutions of 10% vol/vol and 30% vol/vol at 4 times per day for CAM-101 are expected to provide a safety margin with respect to TGF-β1 of 5fold and 1.6-fold, respectively

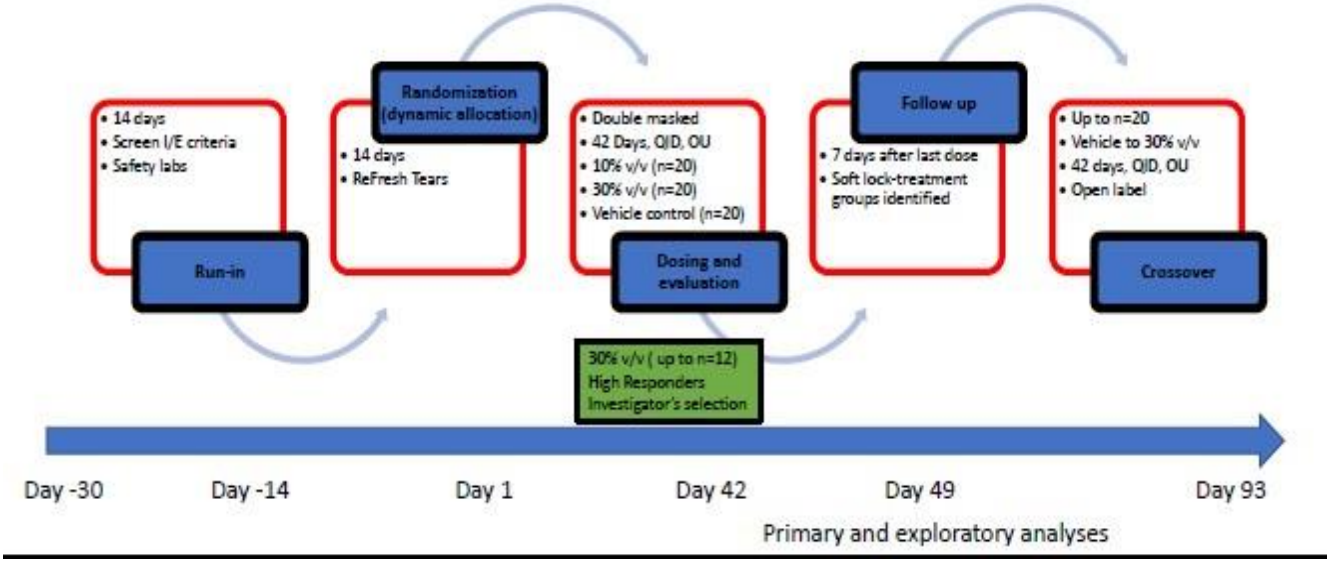
Protocols reported for the preparation and usage of autologous and platelet rich plasma serum drops for primary DED and DED secondary to GvHD also vary considerably as to optimal treatment length prior to assessment of safety and efficacy. The reported range for improvement in DED signs and symptoms has been 1 to 3 months. Importantly, this Study's Sponsor has not uncovered any studies of serum drops for DED or other corneal diseases or conditions from the mid-1980s to present that report any significant adverse events. In one study 2 of 12 participants had signs of conjunctivitis with negative culture that resolved (Pan et al., 2017). It remains unclear, however, from these studies whether serum drops actually require up to 3 months to establish efficacy. Numerous studies involving serum drops for DED report no safety issues and subsequent improvements in outcomes after approximately 1 month of treatment (Ogawa, Okamoto et al. 2003, Na and Kim 2012)]. As a result, the CAM-101-01 is designed to assess both safety and exploratory efficacy at 21 days (3 weeks) and 42 days (6 weeks)—bracketing this 1-month period reported in the literature. The primary and secondary outcomes will be evaluated after 6 weeks of dosing with CAM-101 in the study population.

8.4 Study Flow

Investigational Product will be administered to eligible patients after completion of the Run-in period with artificial tears (see **Figure 2**). Ocular examinations and questionnaires to assess "Symptom Severity" (a composite score frequency of artificial tear use, OSDI, ocular discomfort and ocular symptom frequency rating by VAS) shall be conducted on Day 0 within 24 hours of the end of the Run-in period. The composite results shall be used for dynamic allocation of patients to one of 3 treatment groups before the first dose on CAM-101 investigational product.

Special populations of patients who experience significant improvement-defined as >50% overall improvement in the Symptom Severity score (e.g. an improvement in 3 of 5 components: OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, frequency of use for artificial tears OU, and overall clinical impression) on Refresh Plus® tears alone during the Run-in period may be allocated to treatment with 30 vol/vol % FD hPL and followed for 42 days by discretion of the Investigator. These patients will be selected at Day 0 at the end of the Run-in. This special population of 'high responders' treated with FD hPL will be limited to 12 patients throughout the study. Additional 'high responders' will be excluded from the study at Day 0**.** Their selection into the study will be tracked by the IWRS system. These patients will participate in all study visits 1-4. Their safety and tolerability data will be included in the full data set, but their preliminary efficacy outcomes (secondary objectives) will not be included with the full analysis set.

Figure 2: Study Flow CAM-101 Phase 1/2



All patients will be treated for 42 days (6 weeks) and followed up at Day 49 ± 3. Top-level data will be unmasked between the final dosing visit and the Follow-up visit on Day 49 ± 3 so that patients in the vehicle control treatment groups can be identified. These patients will be offered the opportunity to continue in the open-label study for an additional 42 days of treatment. All other patients will be dismissed at Day 49 ± 3.

9 SELECTION AND WITHDRAWAL OF PATIENTS

9.1 Patient Inclusion Criteria

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

1. Male or female patients, of age 18 years (inclusive) or older at the time of signing the ICF;

2. Diagnosis of DED secondary to GvHD following allogeneic hematopoietic stem cell transplantation as determined by medical history

3. For females:

a. Be of non-child-bearing potential. Surgically sterilized (e.g., hysterectomy or bilateral oophorectomy) for at least 6 months prior to screening or postmenopausal (postmenopausal women must have no menstrual bleeding for at least 1 year prior to screening) and menopause will be confirmed by a plasma FSH level of >40 IU/L) ***or***

b. Women of childbearing potential must be non-lactating and agree to use a highly effective acceptable form of birth control (e.g., established hormonal birth control plus a barrier method, double barrier method: intrauterine device plus condom or spermicidal gel plus condom) from 21 days prior to dosing until 7 days after dosing, ***and***

c. Women with a negative pregnancy test (β-hCG assay) in urine at screening and Day 1 predose;

4. Schirmer tear test with anesthesia <7 mm/5 min in at least one eye during screening;

5. Willingness and and ability to undergo, and return for, all scheduled study-related visits through Follow-up (**Appendix 21.1**);

6. Willingness and and ability to provide written Informed Consent consistent with privacy language as per national regulations (e.g., HIPAA authorization) and which signature may be obtained from the patient or legally authorized representative prior to any studyrelated procedures (including withdrawal of prohibited medication);

7. Willingness to communicate with the Investigator and site staff and comply with all study procedures and requirements;

8. Agreement not to participate in another interventional study while participating in this study.

9.2 Patient Exclusion Criteria

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

1. Any abnormal lid anatomy or blinking function in either eye;

2. Any history of other ocular disease requiring topical ocular treatment other than artificial tears and/or Restasis (cyclosporine ophthalmic emulsion; Allergan Irvine, CA) or Xiidra® (lifitegrast, Shire, Lexington, MA). Patients currently using ocular hypotensive therapy as a result of glaucoma are allowed as long as only 1 drug is used to control pressures. Patients currently using Restasis® or Xiidra® for conditions other than DED (e.g., allergies) are not allowed;

3. Previous intraocular or ocular laser surgery within the past 3 months or any refractive surgery procedure within the past 6 moths of the screening visit in either eye;

4. Any relevant ocular anomaly interfering with the ocular surface, including active ocular herpes simplex infection, recurrent corneal erosion, symptomatic epithelial basement membrane dystrophy, mucus fishing syndrome, giant papillary conjunctivitis, postradiation keratitis, Stevens-Johnson syndrome, corneal ulcer, abnormalities of the nasolachrymal drainage system, chemical injury, diagnosed significant anterior blepharitis and/or progressive pterygium, or any other condition(s) associated with or causing dry eye;

5. Presence or history of any ocular disorder or condition, including ocular surgery (including palpebral and cataract surgery, trauma), infection (viral, bacterial, fungal), disease or inflammation not associated with dry eye unless disorder or disease is:

    a. Stable for at least 3 months before the Screening Visit; and

    b. As determined by the Investigator not likely to impact or possibly interfere with the interpretation of study results.

6. History of ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye;

7. Known hypersensitivity to one of the components of the study or procedural medications (e.g., proparacaine, fluorescein, lissamine green, Refresh Plus®);

8. Inability to refrain from contact lens wear during the study, including the 2 week Run-in period;

9. Anticipated need for temporary or permanent punctal plugs during the study, except if punctal plugs have been in place for at least 2 weeks prior to Screening, in which case the plugs are allowed to remain in place during the study. If plugs should fall out during the course of the study, the instance will be recorded and the plug(s) may be replaced at the investigator's discretion. Plugs may not be placed in eyes that did not have plugs in place at the screening visit.

10. Ocular or clinically significant systemic disease (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease) or condition(s) not stabilized within 1 month (30 days) before Screening or a condition judged by the Investigator to be incompatible or interferes with the study results;

11. Inability or unwillingness to discontinue use of autologous serum eye drops or platelet rich plasma eye drops during the 2 week washout period and the duration of the study;

12. Anticipated change in the use or dose of Restasis®, Xiidra®, or artificial tears within 14 days before Screening or during the study. If currently taking Restasis®, Xiidra®, or artificial tears, treatment(s) for DED can continue throughout the study without a change in dose. If currently using Restasis® or Xiidra® for conditions other than DED, then patient will be excluded from

study. If not currently taking Restasis®, Xiidra® or artificial tears, the use of these drugs cannot begin during the study;

13. Anticipated change in the patient's use of or dosage of systemic medications that could affect tear function (e.g., antihistamines, tricyclic antidepressants, anxiolytics, antimuscarinics, beta-blocking agents, phenothiazines, tacrolimus, sirolimus, etc.) during the study. If currently taking any of these drugs, treatment(s) can continue throughout the study without a change in dose;

14. Pregnancy or breast feeding at the time of study entry;

15. History of clinically significant drug or food allergy;

16. A medical history of positive HIV, hepatitis B or C viral test within 12 months of screening.

17. History or presence as judged by the Investigator, of drug or alcohol abuse to the extent that it might interfere with the candidate's suitability to be in the study as judged by the investigator;

18. Taken any investigational medication and/or participated in any clinical studies within 30 days of screening;

19. Any patient who, in the judgment of the Investigator, may not be able to cooperate fully with the study staff, may have difficulty following some study requirements, or is otherwise not qualified for the study;

20. Any patient who is directly involved in the conduct of the protocol.

9.3 Patient Withdrawal Criteria

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

A patient may be discontinued from the study for any of the following reasons:

- Noncompliance with protocol as judged by the Investigator and/or the Sponsor;
- Incorrect enrollment of the patient (requires discussion with the Sponsor);
- An AE that presents an unacceptable consequence or risk to the patient in the judgment of the Investigator, Sponsor, or the Medical Monitor;
- Lost to follow-up; Withdrawal of consent;
- Judgment of the Investigator.

9.3.1 Stopping Rules

Further administration of the study medication to a patient will be terminated under the following circumstances:

1. A patient in a dose group experiences a serious adverse event (SAE) that is possibly drug-related;
2. A patient withdraws consent to continue in the study.

Further administration of the study medication to a dose group will be terminated under the following circumstances:

1. Two or more patients in a dose group experience a drug-related SAE;
2. The study is prematurely discontinued by the Sponsor or regulatory authority.

Further administration of the study drug by a study site may be discontinued under the following circumstances:

1. Failure of the Investigator to comply with applicable current regulations and GCPs;
2. Failure of the Investigator to accrue patients into the study at an acceptable rate;.
3. Failure of the investigator to comply with the provisions of the experimental protocol.

9.4 Patient Replacement Criteria

Patients may be replaced in any dose group after drop out after consultation with the Sponsor and the Medical Monitor. Replacements shall be made on a case-by case basis. Replacements will be randomized with IWRS using dynamic allocation by site and "Symptom Severity" as measured by a composite score of OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, and frequency of use for artificial tears in OU.

10 TREATMENT OF PATIENTS

10.1 Description of Study Drug

The drug substance or active biologic ingredient, FD hPL, is a liquid product derived from coagulated blood provided as a lyophilized fibrinogen depleted substance to the patient at concentrations of 10 vol/vol% or 30 vol/vol% in PlasmaLyte-A. The formulated drug product, CAM-101, is a preservative-free ophthalmic drop that is manufactured under Good Manufacturing Practice conditions at a facility in Barco, Portugal owned and operated by Stemmatters Biotecnologia e Medicina Regenerativa, Sponsor's Contract Manufacturing Organization (CMO) and is intended for ocular instillation.

10.2 Study Eye Determination

Both eyes shall be entered into the study.

10.3 Concomitant and Prohibited Medications

Any prior and concomitant medications taken in the past 6 months must be recorded in the eCRF.

Prohibited

Wearing contact lenses during the Run-in period or during the study will not be permitted. Other types of DED remedies (e.g. autologous serum, PRP serum) are not allowed during the study. Any medications taken during the study must be recorded in the eCRF. Patients must refrain from recreational consumption of marijuana in any form from 21 days before first dose until 7 days after the last dose.

Rescue Pain Medication

Patients are allowed to use pain medications as prescribed by a physician.

10.4 Diet and Activity

There are no limitations on consumption of food or food types.

Patients will maintain their usual level of physical activity during the study and will maintain a normal sleep (at least 6-8 hrs./night) and wake pattern during a 24-hour cycle.

10.5 Treatment Compliance

Significant Investigational Product or study procedure non-compliance (<80% or >120% of expected dose as determined by number of empty bottles returned and patient diary) may also be a reason to withdraw a patient from the study if study evaluations are significantly confounded or if further participation would be injurious to the patient's health or well-being in the opinion of the Investigator in consultation with the Sponsor. If a patient is non-compliant in the opinion of the Investigator, the Sponsor should be consulted for instructions on handling the patient.

10.6 Randomization and Masking

10.6.1 Randomization

The CAM-101-01 study is a randomized, vehicle-controlled double-masked study for the first 42 days of dosing followed by an open-label, active only, crossover phase for the second 42 days of dosing for subjects who received vehicle during the first 42 days. Patients will be dynamically allocated 1:1:1 to receive FD hPL test (10 vol/vol % or 30 vol/vol %) or vehicle control product based on a composite score for "Symptom Severity (defined as: OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, frequency of use for artificial tears OU)" after Run-in. Randomization will insure that each dose group will have equivalent ranges of severity as measured by a composite of OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, and frequency of use for artificial tears taken on Day 0 or within 24 hours of the end of the Run-in period for each patient at each study site.

Randomization will be done centrally by IWRS at the visit on Day 1. Dynamic allocation to each of the 3 treatment groups on the basis of "Symptom Severity" will be performed for each site. Special populations of patients who have a significant improvement-defined subjectively as having >50% overall "improvement in Symptom Severity (e.g. an improvement in 3 of 5 components: OSDI score, ocular discomfort VAS, ocular symptom frequency VAS, frequency of use for artificial tears OU, and overall clinical impression)" may be assigned to receive 30 vol/vol % FD hPL at the investigators discretion. A maximum of 12 patients throughout the study and across all sites shall be enrolled in this way. Additional 'high responders' will be excluded from the study at Day 0. All others will be dynamically allocated. The randomization number will be assigned based on information obtained from the IWRS Technology.

10.6.2 Unmasking

The study will be double-masked such that neither the Investigator, Sponsor's study management team, clinical staff, nor the patient will know which agent is being administered at Day 1. To maintain masking and minimize bias the Investigator, sub-Investigator(s), all designated readers and graders, the patient, the Sponsor and monitors involved in reporting, obtaining and/or reviewing the clinical evaluations for a patient will not be aware of the specific randomization assignment for that patient. The independent statistician and research pharmacist shall remain unmasked.

10.6.3 Unmasking for Open label Cross-over Study

The unmasked research pharmacist shall identify all patients that were evaluated with vehicle control eye drops by the 6-week visit. The patients will be identified after the end of the 6 weeks dosing visit (Visit 3) and before Follow-up (Visit 4; Day 49 ± 3). The Investigator will be notified of the patient's treatment group before the Follow-up visit. The allocation of patients to the other two treatment groups will not be revealed at that time. The Investigator shall determine the continued eligibility and offer patients who were assigned to vehicle control group and continue to be eligible the opportunity to continue in the open-label crossover study. These patients will be given active CAM-101 to take home at the end of the Follow-up visit (Visit 4; Day 49 ± 3). All others will be dismissed from the study.

10.6.4 Unmasking in Exceptional Cases

At other times in the study the mask shall only be broken in exceptional circumstances. The Investigator should not unmask any trial participants' randomization assignment without the Sponsor's approval, unless immediately required, or in response to a SAE. In a medical emergency, when the management of a patient's condition requires knowledge of the treatment assignment, the Investigator will inform the Medical Monitor and the Sponsor within 24 hours to discuss the emergency and obtain the study treatment assignment from the unmasked research pharmacist. The Investigator shall use his/her discretion to conduct any additional assessments. The additional assessments shall be recorded in the eCRF.

If possible, the medical emergency should be discussed with the Medical Monitor prior to the disclosure of the treatment assignment, or as soon as possible. In a non-emergency situation, when a code break is required, it must be discussed with the Medical Monitor and the Sponsor and approved in writing. If the randomization code for a patient is broken, the Investigator will record the date and reason for breaking the mask for that patient in the source documents. The patient(s) will be withdrawn from the study and the Investigator shall complete both the Early Termination and Follow-up procedures. The Sponsor will exercise its discretion to replace (see **Section 9.4**) any patient while considering the overall safety of the dose group.

11 STUDY DRUG MATERIALS AND MANAGEMENT

11.1 Study Drug

The CAM-101 drug product is a thin clear, preservative-free ophthalmic drop (**Table 7**). The CAM-101 vehicle is comprised of salts and electrolytes from the list of excipients that are GRAS.

Table 7: Investigational Product

	Active	**Vehicle**
Product name:	CAM-101	CAM-101 vehicle
Chemical name, active biologic ingredient:	FD hPL (fibrinogen-depleted human platelet lysate)	PlasmaLyte-A
Molecular formula:	NA	NA
Dosage form:	0.5 mL product in each 1 mL bottle	0.5 mL vehicle in each 1 mL bottle
Unit dose	10 vol/vol% and 30 vol/vol%	
Route of administration	Ocular Instillation	Ocular Instillation
Physical description	Clear, colorless solution with no visible particles.	Clear, colorless solution with no visible particles.
Inactive ingredients:	PlasmaLyte-A as diluent. Final pH 7.0 (+/-± 0.8)	Per 100 mL Sodium Chloride, USP: 526 mg Sodium Gluconate: 502 mg Sodium Acetate Trihydrate, USP: 368 mg Potassium Chloride: 37 mg Magnesium Chloride: 30 mg Adjusted to pH: 7.4 (6.5-8.0)
Manufacturer	Of ABI: Stemmatters, Biotecnologia e Medicina Regenerativa, SA, Barco, Portugal.	Of PlasmaLyte-A (Vehicle): Baxter Healthcare, Deerfield, IL.

CAM-101 is a liquid product provided to the patient at concentrations of 10 vol/vol% or 30 vol/vol% fibrinogen-depleted human platelet lysate (**Table 8**). The vehicle product will consist of PlasmaLyte-A formulated for eye dropping. PlasmaLyte-A is a sterile, nonpyrogenic isotonic solution in a single dose container. Both the vehicle and active test products will be packaged in single use 1mL Wheaton low-density polyethylene (LDPE) dropper bottles (Wheaton Industries,

Inc., Millville, New Jersey) with white caps. The drop size is approximately 0.035 mL (35 □L). Patients will be instructed to dose both eyes QID with 1 drop per eye.

Table 8: Investigational Product Dispensed and Storage per Drop

Group	FD hPL (volume mL) in 1 mL Wheaton Bottle	Dose (both eyes)	Vehicle Solution (volume mL) in 1 mL Wheaton Bottle
1	10 vol/vol% FD hPL	1 gtt/QID	
2	30 vol/vol % FD hPL	1 gtt/QID	
3		1 gtt/QID	100% PlasmaLyte-A

Note: gtt = a single drop; QID = four times a day.

Patients will be instructed to store all Investigational Product frozen in their home freezer at – 20°C ± 3o Centigrade (i.e., –9°F to 1°F, typical home freezer temperature). Patients will be advised to thaw the next day's dosage (4 bottles) overnight, the day before use in their refrigerator or during the day of use. Specific handling, storage, thawing, and preparation of Investigational Product can be found in the Investigational Brochure and **Appendix 21.13**.

11.2 Study Drug Packaging and Labeling

Study medication will be packaged in a 32-pack carton containing a 21-Day supply of active FD hPL or vehicle plus a 4 bottle (extra day) surplus. Three new cartons will be dispensed at Day 1 (randomization) and Day 21 of the core study and at Day 49 and Day 70 of the open-label crossover study. Each day's dosage of Investigational Product will be provided to patients in special 1 mL capacity LDPE 3-piece, single-use dropper bottles. The bottle's LDPE is certified by the manufacturer (Wheaton) as stearate-residue free, a requirement for use in ophthalmic products.

Both CAM-101 test product and vehicle control will be packaged in identical bottles. Artificial tears (Refresh Plus) will be provided in the commercial packaging. **Appendix 21.7** contains sample language for labels that will be used for randomization purposes only, but that will remain masked as to which labels are assigned to which Investigational Product to the Investigator, clinical site, and patient throughout the core study. The primary packages and labels of the study medications for active treatment and vehicle control will remain indistinguishable for masking purposes (see **Appendix 21.7**).

All investigational medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at the Sponsor's CMO (Stemmatters) in accordance with the Sponsor's designee's Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each bottle as well a one-week supply carton of Investigational Product will bear a label conforming to regulatory guidelines; GMP will identify the contents as an Investigational Product.

The CAM-101 (FD hPL test product) and vehicle control will be supplied to the sites by the Sponsor (and by the sites to patients) in 32-pack cartons. Each container will provide sufficient Investigational Product (plus 4 extra bottles or a single extra day's dosage) sufficient for a week's supply of product at the recommended study dosage. Patients will be given, based on centralized randomization, three cartons of Investigational Product at both Day 1 (Baseline Exam) and Day 21

(First Treatment Exam) sufficient to get them through each of the two planned 21-day treatment periods between exams consistent with the 42-day study. Patients in the open-label crossover study will likewise be given three cartons of Active Investigational Product at both Day 49 (Visit 4) and Day 70 (Visit 5)-sufficient to get the patient through each of the two planned 21-day open-label treatment periods. Patients will be instructed to store all Investigational Product in their home freezer in original cartons. Patients will also be provided thawing instructions and be instructed to return all used and unused Investigational Product back to their study site at Day 21 and Day 42 after dosing. Used and unused bottles should be returned in the original Investigational Product cartons provided to patients on Days 1 and 21.

11.3 Study Drug Storage

Study medication should be stored in the freezer and thawed before use.

11.4 Study Drug Preparation

Patients will be instructed on appropriate hygiene and eye drop dosing technique for single use drops by clinic staff as shown in **Appendix 21.8**. Patients will self-administer CAM-101 (FD hPL) or vehicle control under the supervision of the medication coordinator for the first dose.

11.5 Administration and Missed Doses

At dosing, a single drop (i.e., 35 µL/drop) will be instilled OU. Study medication should be stored in the freezer at or below 0 degrees (0º F). A day's supply of medication (4 bottles) can be transported in the cups that are provided.

Instruction for preventing potential cross-infection from touching the bottle dropper to the skin or eye will be emphasized by coaching each patient about the importance of not touching the eye with the bottle nozzle. Patients will be reminded to administer 1 drop to each eye. If the drop misses the eye, the patient should re-administer the drop.

Patients will also be instructed on the proper methods for recording the times for at-home dosing when filling out the dosing diary. The medication coordinator will discuss the time of study drug administration with each patient. Clinic staff will coach the patients to dose themselves at approximately the same time every day ± 3 hrs. If a dose is missed and the 3-hour window is exceeded, then the next dose should be administered on time. The missed dose should be recorded in the patient diary. The actual time of study drug administration should be noted and recorded for each dose that the patient took (see **Appendix 21.8**).

11.6 Study Drug Accountability

All study medication used during the course of the study must be accounted for on a drug accountability form. Investigational study medication orders, records of receipts, dispensing records, and inventory forms will be examined and reconciled. At each of the two follow-up visits, patients

will return all used and unused bottles in their respective cartons to the clinic for accountability purposes. Accountability will be ascertained by performing reconciliation between the amount of study Investigational Product (# cartons and bottles) sent to the site, the amount used and unused at the time of reconciliation. Unmasked site staff will be queried about any discrepancies. No Investigational Product or 32-pack cartons will be discarded at or by the site, but returned to Sponsor's contract research organization (CRO) for final compliance tabulations. Following these final tabulations, all Investigational Product will be discarded/destroyed by the CRO.

Study drug shipment records will be verified and accountability performed by comparing the shipment inventory sheet to the actual quantity of Investigational Product received at the site. Accurate records of receipt and disposition of the Investigational Product (e.g., dates, quantity, patient number, cartons used, cartons unused, etc.) must be maintained by the unmasked pharmacist or his/her designee.

11.7 Study Drug Handling and Disposal

Unless otherwise directed, at the end of the study all unused Investigational Product dispensed to and returned from patients medications must be directly shipped from the clinical site to the Sponsor's CRO for final compliance tabulations and for disposal. All non-dispensed Investigational Product will be shipped frozen from each site back to the Sponsor at an address to be provided. **Note: Investigational Product should not be disposed of prior to full accountability by the site and the Sponsor's clinical research associates (CRA). The Sponsor will provide permission to dispose of the Investigational Product to the CRO in writing.** The clinical site will provide a copy of all completed Investigational Product disposition forms to the Sponsor after the completion of the study.

Current ICH GCP Guidelines require the Investigator to ensure that Investigational Product deliveries from the Sponsor are received by the Investigator (or designee) and are handled and dispensed to patients as follows:

- All deliveries and allotments of Investigational Product are to be recorded;
- All Investigational Product is to be handled, stored, and dispensed to patients according to labeled storage requirements (i.e., frozen at –20±3°C or at or below 0°F). In addition, Investigational Product will be kept at each study site in a pharmacy or other locked and secured frozen storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense these study products;
- Expiration dating of CAM-101 is "To Be Determined" through ongoing stability study protocols defined in IND 17669. Only Investigational Product meeting stability study pre-defined limits will be distributed to clinical sites and/or dispensed to study subjects;
- All Investigational Product whether dispensed or not dispensed will be accounted for by the study Sponsor designee (i.e., CRO) at the completion of each of the 21 and 42day exams in both the core and open label studies. All used and unused

Investigational Product in inventory at each study site will be segregated, accounted for and returned to Sponsor's CRO (or if involving un-dispensed product, directly to the Sponsor or designated representative);

- Investigational Product inventory and accountability records (Product Accountability Records) for the storage, dispensing and return of all Investigational Product will be kept by the Investigator/or designee. It must be possible to reconcile delivery records with those of used and/or returned Investigational Product. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.

12 SCHEDULE OF EVENTS

12.1 Study Periods

12.1.1 Screening Period (Days –30 to –14)

Patients should be instructed not to administer any eye drop less than 2 hours before their screening visit and to refrain from contact lens use on the day of screening and throughout the study

Screening procedures will be as follows:

- Signing of the ICF
- Eligibility criteria (inclusion and exclusion criteria check)
- Demographic characteristics
- Medical/surgical/ocular history
- Height, body weight, and calculated BMI (**Section 13.4**)
- Vital signs (body temperature, heart rate, blood pressure, and respiratory rate; **Section 13.3**)
- Review of prior and concomitant medications
- Brief physical examination (appearance, mood, affect; **Section 13.5**)
- Ocular examinations (in this order): **Appendix 21.1**
- Frequency of artificial tear use
- Ocular discomfort scale (**Appendix 21.2**)
- Ocular Surface Disease Index (OSDI; **Appendix 21.3**)
    - Symptom frequency scale (burning stinging, itching, foreign body sensation, eye discomfort, dryness, grittiness, photophobia, pain; **Appendix 21.2**)
    - Tear osmolarity (patient must refrain from administrating any tear supplements within two (2) hours of this test; **Appendix 21.4**)
    - Visual acuity: Best corrected distance visual acuity (ETDRS protocol; **Appendix 21.11**)

- External eye exam (eye color, eyelid position, redness/irritation; **Appendix 21.9** and **Appendix 21.10**)
- Slit lamp biomicroscopic exam (eyelid margins and lashes, tear film and function, conjunctiva, sclera, cornea, and assessment of central and peripheral anterior chamber (anterior chamber depth, iris, lens, anterior vitreous for cells and flare) examinations will be performed prior to mydriasis [**Appendix 21.1**]) ○ Tear break up time (**Appendix 21.1**) ○ Corneal fluorescein stain (**Appendix 21.1** and **Appendix 21.12**) ○ Conjunctival lissamine green stain (**Appendix 21.1** and **Appendix 21.12**) ○ Schirmer's test with anesthesia (**Appendix 21.1**)
- IOP (after all assessments of the ocular surface and cornea have been completed; **Appendix 21.1**) ○ Dilated fundus examination (**Appendix 21.1**)

- Pregnancy test for females of childbearing capacity (urine; **Appendix 21.1**)
- Plasma follicle stimulating hormone (FSH**)**
- Alcohol and drug abuse screen (questionnaire **Table 13)**
- Safety laboratory tests (hematology)
- Confirm medical history no HIV and Hepatitis B and C (past 12 mos**)**
- Adverse event surveillance (surveillance begins upon signing of Informed Consent and Commencement of Study Assessments).

12.1.2 Run-in Period (Day –14 to 0)

Patients will be required to washout of all prohibited medications and stop wearing contact lens. Patients will be given a diary and taught how to dose themselves with Refresh Plus® tears for 14 days prior to randomization.

- Confirm medical history on Day –14
- Provide patient with Diary on Day –14
- Dispense 14-day supply of preservative-free artificial tears (Refresh Plus®) on Day – 14
- Frequency of artificial tear use (Day 0)

- Ocular discomfort scale (Day 0, **Appendix 21.2**)
- Ocular Surface Disease Index (OSDI; Day 0, **Appendix 21.3**)
- Symptom frequency scale (burning stinging, itching, foreign body sensation, eye discomfort, dryness, grittiness, photophobia, pain; Day 0, **Appendix 21.2**)
- Dispense new 14-day supply of preservative-free artificial tears (Refresh Plus®) on Day –14
- Review patient Diary (Day 0)

12.1.3 Procedures on Day 1

12.1.3.1 Predose

- Eligibility criteria (inclusion and exclusion criteria review)
- Medical/surgical/ocular history review
- Vital signs (body temperature, heart rate, blood pressure, and respiratory rate; to be completed 30±10 mins before dose; **Section 13.5**)
- Concomitant medications review
- Brief physical examination (appearance, mood, affect; **Section 13.5**)
- Ocular examinations (in this order): **Appendix 21.1** ○ Frequency of artificial tear use
    - Visual acuity: Best-corrected distance visual acuity (ETDRS protocol) (**Appendix 21.1** and **Appendix 21.11**)
    - Tear osmolarity (patient must refrain from administrating any tear supplements within two (2) hours of this test; **Appendix 21.4**)
    - Slit lamp biomicroscopic exam (ocular surface; conjunctiva, sclera, cornea;

      Appendix 21.1) ○ Tear break up time (**Appendix 21.1**) ○ Corneal fluorescein stain

      (**Appendix 21.1** and **Appendix 21.12**) ○ Conjunctival lissamine green stain

      (**Appendix 21.1** and **Appendix 21.12**) ○ Schirmer's test (**Appendix 21.1**)

- IOP (after all assessments of the ocular surface and cornea have been completed (**Appendix 21.1**)

- Randomization by IWRS
- Adverse event surveillance
- Dispense new 21-Day supply of preservative-free artificial tears (Refresh Plus)
- Review diary

12.1.3.2 Day 1 First Dose

- Dispense 21-Day supply of Investigational Product
- Dispense new 21-Day supply of preservative-free artificial tears (Refresh Plus®)
- Thaw one vial (at least 1.0 hr. before dose)
- Instill Investigational Product OU at least 30 minutes before assessments
- Adverse event surveillance
- Diary review

12.1.3.3 Day 1 First Dose (at least 30 min. post dose)

- Instruct patient not to use artificial tears within 30 minutes of instilling Investigational Product
- Vital signs (body temperature, heart rate, blood pressure, respiratory rate; within 0.5 hrs (30 minutes) after dose (**Section 13.5**)
- Slit lamp biomicroscopic exam; ocular surface: conjunctiva, sclera, cornea; at least 30 minutes but not greater than 3 hours after the administration of investigative product (**Appendix 21.1**)
- Adverse event surveillance
- Remind patient take the study drug 4 times a day; the fourth dose should be taken before bedtime

- Remind patient not to administer any eye drop, including the Investigational Product or artificial tear, less than 1 hour prior to visit on Day 21 and Day 42.
- Make arrangements for next visit on Day 21
- Dismissal from unit

12.1.4 Dosing and Evaluation Period (Day 21 ± 3 and Day 42 ± 3)

Patients will be instructed to administer the first dose of study drug OU at home. Patient shall not administer any eye drop, including the Investigational Product or artificial tear, less than 15 minutes prior to the clinic visit on Day 21 or Day 42. No artificial tear should be administered for 2 hours before tear osmolarity tests

At home

- Thaw one vial (at least 1 hr. before dose)
- Instill investigative product OU at least 1 hour before being seen at the clinic
- Refrain from artificial tears until 30 minutes after instillation of investigational drugs
- Record time of dosing in diary

At clinic

- Vital signs (body temperature, heart rate, blood pressure, respiratory rate; **Section 13.5**)
- Review concomitant medications
- Brief physical examination (appearance, mood, affect; **Section 13.5**)
- Ocular examinations (**Appendix 21.1**) ○ Frequency of artificial tear and Investigational Product use
    - Visual acuity: Best corrected visual acuity at distance (ETDRS) (**Appendix 21.1** and **Appendix 21.11**) ○ External eye exam (redness/irritation;

Appendix 21.10) ○ Ocular discomfort scale (VAS; **Appendix 21.2)** ○ Ocular Surface Disease Index (OSDI; **Appendix 21.3**)

- Symptom frequency scale (burning stinging, itching, foreign body sensation, eye discomfort, dryness, grittiness, photophobia, pain; **Appendix 21.2**)
- Tear osmolarity (patient must refrain from administrating any tear supplements within two (2) hours of this test**; Appendix 21.4**)
- Slit lamp biomicroscopic exam (eyelid margins, iris, lens, anterior vitreous for cells and flare; **Appendix 21.1**) ○ Tear break up time (**Appendix 21.1**)
- Corneal fluorescein stain (**Appendix 21.1** and **Appendix 21.12**) ○ Conjunctival lissamine green stain (**Appendix 21.1** and **Appendix 21.12**) ○ Schirmer's test (**Appendix 21.1**) ○ IOP (**Appendix 21.1**) ○ Dilation with mydriatic drops (Day 42 ± 3 only) ○ Dilated fundus examination (Day 42 ± 3 only) ○ Investigators global examination (Day 42 ± 3 only; **Appendix 21.1**)

- Pregnancy test for females of childbearing capacity (urine; Day 42 ± 3 only)
- Adverse event surveillance
- Diary review
- Return old bottles /dispense new 21 day supply of artificial tear (do not dispense on Day 42 ± 3)
- Dispense 21-day supply of Investigative Product; (do not dispense on Day 42 ± 3)
- Remind patient take the study drug 4 times a day; the fourth dose should be taken before bedtime (Day 21 ± 3 only)
- Remind patient not to administer any eye drop, including the Investigational Product or artificial tear, less than 1 hour prior to next visit.
- Make arrangements for next visit on Day 42 (Day 21 ± 3 only)
- Make arrangements for Follow-up visit (Day 42 ± 3 only)

- Dismissal from unit

12.1.5 Procedures on Day 49 ± 3 (Follow-up)

Patients will return to the study unit on Day 49 ± 3 for Follow-up evaluations. Investigator will obtain identifying information on patients who received control product. Adverse events will be monitored until Follow-up Day 49. Concomitant medication review will be also performed through Follow-up Day 49. The patient may be discharged from the study if no ongoing clinical or laboratory AEs are present. Patients with ongoing clinically significant AEs may remain in the study unit at the discretion of the Investigator. Subjects who received control agent will be given the opportunity to take active study medication for 42 days.

- Vital signs (body temperature, heart rate, blood pressure, respiratory rate)
- Review of concomitant medications
- Brief physical examination, (appearance, mood, affect; **Section 13.5**)
- Ocular examination signs and symptoms (in this order): (**Appendix 21.1**)
    - Visual acuity: best corrected visual acuity at distance (ETDRS; **Appendix 21.1** and **Appendix 21.11**)
    - External eye exam (ocular signs of redness; **Appendix 21.1** and **Appendix 21.10**)
    - Slit lamp biomicroscopic exam (eyelid margins, iris, lens, anterior vitreous for cells and flare; **Appendix 21.1**)
- Pregnancy test for females of childbearing capacity (urine)
- Safety laboratory tests (hematology, serum chemistry, and urinalysis) for patients who have experienced SAEs only
- Adverse event surveillance
- Collection of diary
- Unmasking
- Dismissal of patients in 10 and 30 vol/vol% dose groups from study

Patients who had received vehicle during the first 42 days of doses and who continue to be eligible will be invited to receive open-label treatment with active test product

- Dispense 21 day supply of active investigative product; (do not dispense on Day 70 ± 3)
- Remind patient take the study drug 4 times a day; the fourth dose should be taken before bedtime
- Remind patient not to administer any eye drop, including the Investigational Product or artificial tear, less than 1 hour prior to next visit.
- Make arrangements for next visit on Visit 5 (Day 70 ± 3)
- Make arrangements for final visit on Visit 6 (Day 91 ± 2)

12.1.6 Early Termination

Discharge from the study unit and/or the study will be decided after consultation between the Investigator and Sponsor. For patients who terminate early, collection of all data from Day 42 procedures should be completed. If there are no ongoing clinical or laboratory AEs, the patient will be ***discharged from the study***.

12.1.7 Patient Crossover (Days 50 ± 3 to 91 ± 2)

- Follow study instructions as outlined in 12.1.4
- Make arrangements for next visit on Visit 5 (Day 70 ± 3)
- Make arrangements for final visit on Visit 6 (Day 91 ± 2)
- Dismissal from study

13 STUDY PROCEDURES

13.1 Demographic/Medical History

A complete medical history will be obtained from each potential patient during the Screening Period of this study as part of the eligibility assessment. Demographic information, including age, gender (male/female), race, ethnicity, eye color, height, body weight, BMI, and date of Informed Consent will be recorded. A urine pregnancy test will be administered at entry if the Investigator determines this is necessary

Any worsening of **existing conditions** after signing of the Informed Consent and prior to dosing with Refresh Plus artificial tears will be recorded on the Medical History page of the eCRF.

Any **new conditions** reported after signing of the Informed Consent and dosing with Refresh Plus artificial tears will be reported as adverse events.

Current alcohol, marijuana, and tobacco use will be recorded in the eCRF.

13.2 Ocular History

A complete ocular history will be obtained from each potential patient during the Screening Period of this study as part of the eligibility assessment. The ocular history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures). Any new conditions reported prior to Run-in dosing with Refresh Plus artificial tears will be reported on the Medical History page of the source document and entered into the eCRF. A worsening of an existing condition will be recorded on the AE page of the eCRF.

13.3 Vital Signs

Vital signs will be measured after the patient has been sitting for approximately 3-5 minutes. Body temperature, heart rate, blood pressure, and respiratory rate will be recorded.

13.4 Weight, Height, and Body Mass Index

Body height and weight will be measured and BMI will be calculated at the Screening assessment and recorded in standard or metric measure. An attempt should be made to use the same scale and conditions.

13.5 Physical Examination

The brief physical examination will include the following elements: general appearance, mood, and affect (mental status).

13.6 Ocular Examinations

All ophthalmic AEs or any changes detected in the following assessments will be monitored during the course of the study. Severities of symptoms (ocular discomfort and frequency) or objective signs e.g. hyperemia, cornea staining with fluorescein and conjunctival staining with lissamine green will be evaluated using the grading scales provided for each ophthalmic assessment. All examinations prior to IOP measurements should be made without dilation of the pupil. The timing of remaining study procedures can be adjusted at the Investigator's discretion.

If a patient experiences a clinically significant ocular adverse event, the ophthalmic specialist at the site may perform additional ocular examinations. After adequate reversal of dilation, patients will be given post-mydriatic glasses if needed and appropriate warnings against driving after dilation.

The following assessments shall be performed:

- Visual acuity as measured by best-corrected distance visual acuity using ETDRS protocol (**Appendix 21.1** and **Appendix 21.2**)
- External eye examination as measured by: (a) eye color matching, color (**Appendix 21.9**); (b) position and character of eyelids, lashes, lacrimal apparatus and tear function, (c) globe position, and (d) pertinent facial features
- Ocular discomfort scored on a visual analogue scale of 0-100 (**Appendix 21.1** and **Appendix 21.2**)
- Ocular surface disease index evaluated on a scale of 0-100 (**Appendix 21.1**)
- Symptom frequency; evaluates the frequency of 8 symptoms on a visual analogue scale of 0-100 (**Appendix 21.1** and **Appendix 21.2**)
- Tear osmolarity as measured using the TearLab® osmometer (**Appendix 21.4**)
- Slit lamp biomicroscopic examination: eyelid margins and lashes, tear film and function, conjunctiva, sclera, cornea, and assessment of central and peripheral anterior chamber (anterior chamber depth, iris, lens, anterior vitreous for cells and flare) examinations will be performed prior to mydriasis (**Appendix 21.1**)
- Tear break up time (**Appendix 21.1**)
- Corneal staining fluorescein as measured using the Oxford scale (**Appendix 21.1**)
- Conjunctival staining lissamine green as measured using the Oxford scale (**Appendix 21.1**)
- Schirmer test without anesthesia (**Appendix 21.1**)
- IOP measurements will be performed with calibrated Goldmann applanation tonometers or other standard devices as long as the same device is used every time (**Appendix 21.1**)
- Dilated fundus examination shall be performed by indirect ophthalmoscopy (**Appendix 21.1)**
- Investigator's global evaluation to evaluate the improvement in signs and symptoms relative to the baseline visit on Day 1 (**Appendix 21.1**)

13.7 Laboratory Assessments

Laboratory urinalysis for pregnancy is required of all women of childbearing capacity at study exit or Follow-up on Day 49 ± 3. Patients who experienced a serious adverse event (SAE) during the study will also be required to receive a safety blood and urine analysis at Follow-up.

13.7.1 Pregnancy Screen

All female patients of childbearing capacity will provide a urine sample to be tested for β-hCG during the Screening Period. A positive result will result in ineligibility for the study. Patients who have a positive result may be reanalyzed only 1 time during a 30-day screening period. Postmenopausal female patients will provide a blood sample to be tested for serum FSH at screening.

A final urine pregnancy check will be required of all women of childbearing age at the last study Visit 3 at Day 42 ± 3. If this visit is missed the test should be conducted at Follow-up or upon early termination.

14 ADVERSE AND SERIOUS ADVERSE EVENTS

14.1 Definition of Adverse Events

All AEs should be monitored and reported in a timely manner on the AE page of the eCRF during the study. AEs will be captured from the time of first administration of the Investigational Product through the follow-up period. If AEs occur, the safety of the study patient should be the main concern.

14.1.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An abnormal laboratory or ophthalmologic finding will only be considered an AE when the Investigator determines the finding to be clinically significant. Thus, any new sign, symptom, or disease, or clinically significant increase in the intensity of an existing sign, symptom or disease, should be considered an AE.

The Investigator will ask an open question to avoid influencing the patient, e.g., “Have you had any new symptoms, illness, or worsening of pre-existing conditions?” Directed questioning and examination will be conducted thereafter when appropriate. This applies to all AEs, including SAEs.

Notes:

*An abnormality found during the Screening and the Predose Periods should be recorded as Medical History, but not as an AE.

*Pregnancy is not to be considered as an AE but as an important medical event, which must be followed up as described in **Section 14.2.4**.

14.1.2 Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed. "Unexpected" refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the drug under investigation. However, an event that is more specific or more severe than described in the IB will be considered unexpected.

14.1.3 Serious Adverse Event

All SAEs will be reported that occur from the day the patients signs the informed consent document until the end of the treatment period (Day 42) or 30 days after the last dose of Investigational Product, whichever occurs last. SAEs that occur within 30 days following the last administration of Investigational Product, regardless of causality, should be recorded and reported immediately to the Sponsor.

An SAE will be followed until it resolves or reaches a clinically stable outcome. If necessary, the Sponsor or designee will contact the patient's personal physician to obtain further details. SAEs that occur more than 30 days after the last dose of investigational product will NOT be collected unless the Investigator determines that the event is related to the investigational product.

An AE is "serious" if in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;*
- Inpatient hospitalization or prolongation of existing hospitalization;**
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;

- Important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.***

Notes:

*An AE is considered "life-threatening" if in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

**The following situations may not by themselves constitute sufficient grounds to be considered as an SAE: (1) hospitalization solely for a diagnostic purpose, even if related to an AE, (2) elective hospitalization for an intervention planned before the patient enrollment in the study, (3) admission to a day-care facility or sleep laboratory.

***An example of an "important medical event" is a potential Hy's Law case (e.g., AST or ALT >3 x upper limit of normal [ULN] and [total bilirubin >2 x ULN or INR >1.5]).

14.1.4 Severity

Severity is a clinical determination of the intensity of an AE and will be determined by the Investigator based on the following classification criteria for all AEs occurring during the clinical study sponsored by Cambium Medical Technologies, LLC.

Mild - Awareness of signs or symptom, but easily tolerated, may require additional therapy

Moderate - Discomfort, enough to cause interference with usual activity and to require intervention or additional therapies

Severe - Incapacitating with inability to work or perform usual activity

Note:

The term "severe" is often used to describe the "intensity" (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.1.5 Relationship to Study Drug

The causal relationship between the Investigational Product and each AE will be determined by the Investigator based on his/her medical judgment in consideration of all relevant factors, including pattern of reaction, temporal relationship, positive dechallenge or rechallenge, concomitant medication, co-existing diseases, and relevant medical history.

The relationship assessment for an AE is to be completed by the Investigator using the following definitions as a guideline for all AEs occurring during the clinical study:

Definite - the AE:

- Occurs in a plausible time relationship to drug administration;
- Cannot be explained by concurrent disease or other drugs or chemicals;
- Follows a clinically reasonable response upon withdrawal (dechallenge); and
- Is confirmed by reappearance of the reaction on repeat exposure (rechallenge).

Probable - the AE:

- Follows a reasonable time sequence to administration of the drug;
- Is unlikely to be attributed to concurrent disease or other drugs or chemicals; and
- Follows a clinically reasonable response upon withdrawal (dechallenge);
- Note: rechallenge data is not required to fulfill this definition.

Possible - the AE:

- Follows a reasonable temporal sequence from drug administration; and Could also be explained by concurrent disease or other drugs or chemicals.
- Note: Information on drug withdrawal may be lacking or unclear.

Not related/remote - the AE:

- Follows a temporal relationship to drug administration, which makes a causal relationship improbable; and in which other drugs, chemicals or underlying disease provide plausible explanations.

14.2 Reporting Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation will be recorded during the study at the investigational site. Any AE, occurring during the AE reporting period regardless of its relationship to the study drug, will be reported immediately on the AE page of the eCRF along with the date of onset, severity, seriousness, action taken, relationship to investigational drug, and outcome.

All AEs will be monitored and recorded for the progress of the event until they resolve or reach a clinically stable outcome, or until it has been determined that the study treatment or participation is not the cause.

Serious AEs and Pregnancy must be reported immediately within 24 hours (**Sections 14.2.2** and **14.2.4**, respectively).

14.2.1 Adverse Event Reporting Period

The Sponsor or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's, or designee's, responsibility to notify the Institutional Review Board (IRB) of any unexpected SAEs, as well as any additional SAEs according to the IRB's policy.

The AE/SAE reporting period starts from the day the patients signs the informed consent document until the end of the treatment period (Day 42) or 30 days after the last dose of Investigational Product, whichever occurs last.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs must be reported during this period. If the clinical site becomes aware of any SAE regardless of causality within 30 days following the last administration of Investigational Product, the SAE should be recorded and reported immediately to the Sponsor. An SAE that occurs more than 30 days *after* the last dose will NOT be collected unless the Investigator considers that the event is related to the Investigational Product.

In addition, the Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any potential drug-related safety information, even after a patient completes the study.

14.2.2 Procedure for Reporting a Serious Adverse Event

Timely, accurate, and complete reporting of an SAE is crucial for the protection of patients. The Investigator, or designee, must enter the serious adverse event information onto the hard copy SAE report form (provided to the site by at the initiation visit) and faxed the form to the Medelis SAE Fax number at (US) 615-297-6539, within 24 hours of the investigator/site staff first becoming aware of the SAE.

- The Investigator will take prompt and appropriate medical action if necessary. The safety of study patients is the first priority.

- Telephone requirement (within 24 hours of the investigator/site staff first becoming aware that the SAE occurred):

    - Telephone the Medical Monitor, or designee, just prior to emailing, faxing, or efaxing the completed investigational site SAE form. Provide the Medical Monitor, or designee, with the Investigator's name, investigational site, your name, the telephone number where you can be reached, the protocol number, patient number, patient initials, date of first dose, date of event, description of event, causality assessment, and counter measures taken.

- Fax requirement (within 24 hours of the investigator/site staff first becoming aware that the SAE occurred):

    - Complete as fully as possible the SAE Form provided by the CRO at study initiation. At a minimum, the intial SAE report should contain the following information:
    - Patient's study ID number ○ Description and date of the event ○ Criterion for seriousness ○ Preliminary assignment of casualty to study drug FD hPL

    Fax the completed SAE form within 24 hours to Medelis **SAE Fax Number (US): 615 297 6539.**

    If the Investigator is unable to verify by fax receipt that the SAE report was sucessfully faxed, the investigator must call the **Medelis SAE Hot line Number** (US): 888 747 1617, to notify Medelis of the incoming SAE fax report, and folow-up with the **Medelis Safety Associate** by phone (US): 615 724 4009 and email (pamela.horowitz@medelis.com)

    Safety Physician:

    M Edmund K. Waller, MD, PhD

    Office Telephone: +1 404-693-7796

    Fax: +1 404-778-3965

    E-mail: ewaller@emory.edu

    Medical Monitor:

R. Doyle Stulting, MD

Mobile: 678-938-1011

Fax:770-804-1679

- The Medical Monitor, or designee, will review the SAE data including the SAE criteria, the relationship to study medication, the expected or unexpected assessment, and inform the Sponsor by phone and e-mail immediately.

- All additional follow-up evaluations must be reported by the site to the Medical Monitor, or designee, immediately by phone and send via fax or e-mail within 24 hours after notification of the additional information. An SAE will be followed until it resolves or reaches a clinically stable outcome. If necessary, the Sponsor or designee will contact the patient's personal physician to obtain further details.

- The Investigator, or designee, is responsible for informing the IRB of any unexpected SAEs, as well as any additional SAEs according to the IRB's policy.

- Any SAE that is serious, related, and unexpected will be promptly reported to regulatory authorities by the Sponsor according to expedited reporting requirements. Subsequent relevant information after the initial submission of the IND Safety Report to the regulatory authorities will be submitted in a follow-up IND Safety Report to the regulatory authorities in the expedited time frame by the Sponsor.

- An SAE that occurs more than 30 days after the last dose will NOT be collected unless the Investigator determines that the event is related to the investigational drug product.

14.2.3 Sponsor's Procedure for Reporting a Serious Adverse Event

Before submitting an IND safety report to the FDA on an expedited basis, the Sponsor will ensure that the AE meets all 3 of the following criteria: it is a suspected adverse reaction, and that it is also serious and unexpected. It is the Sponsor's responsibility to determine whether the AE meets the definition of a suspected adverse reaction.

A suspected adverse reaction means there is a reasonable possibility that the drug caused the AE, which is defined as evidence to suggest there is a causal relationship between the drug and the AE. Any relevant additional information pertaining to a previously submitted IND safety report must be submitted to the FDA as a follow-up IND Safety Report as soon as the information is available.

14.2.4 Procedures for Reporting Pregnancies

Pregnancy is an important medical event, which must be reported in the same manner as an SAE to the Medical Monitor, or designee, by the Investigational Site within 24 hours. If a pregnancy occurs

during the study, study medication must be discontinued immediately. If the pregnancy continues to term, the outcome (i.e., health of the neonate) must be followed-up until outcome to ensure complete collection of safety data on the study medication.

In the case of a pregnancy during the clinical study period, the Investigator is to perform the following steps:

- Stop the investigational drug immediately and withdraw the patient from the study.
- Within 24 hours of the investigator/site staff first becoming aware of a pregnancy, The Pregnancy Questionnaire (provided by the CRO at the initiation of the study) will be completed by the study site Investigator. The Questionnaire will be submitted to Medelis Product Safety via the SAE fax number (615-297-6539). The Medelis Product Safety Associate will forward the documentation to the Medelis Medical Monitor and Cambium for review.
- The progress of the pregnancy will be followed through its outcome. The site investigator should contact the patient's private physician/gynecologist or hospital staff to obtain further details and regular follow-up information. The Pregnancy Questionnaire Form should be completed by the site investigator tri-monthly and submitted to the Medelis Product Safety Associate via the SAE fax number, to provide updates of the progress of the pregnancy to the Medical Monitor and Sponsor.
- Report the progress by tri-monthly updates to the Medical Monitor during the study or to the Sponsor's Medical Director after the completion of the study up to the final outcome of the pregnancy.
- At the completion of the pregnancy, the Pregnancy Outcome form is to be submitted to the Medelis Product Safety Associate via the SAE fax number to report the outcome of the pregnancy. The Medelis Product Safety Associate will manage the query and reconciliation process until the pregnancy documentation is complete. Medelis will notify sites of pregnancy reports as directed by Cambium.
- In the event of a miscarriage, therapeutic abortion, in utero death, or the pregnancy outcome leads to an SAE for the mother, follow the Procedure for Reporting an SAE (**Section 14.2.2**). In the event of a congenital anomaly, an SAE form for the baby must be completed.

At any time, even long after the end of the clinical study, if the Investigator is aware of a developmental abnormality of the baby, he/she must inform the Sponsor.

15 STATISTICS

There are no statistical endpoints in this study. The statistical analysis plan (SAP) for this study will be a pre-specified separate document that provides the information required for this protocol according to the ICH Guideline E9 entitled Statistical Principles for Clinical Trials, 1998.

15.1 Determination of Sample Size

The sample sizes chosen for this study were based upon practical considerations. No a priori statistical assumptions have been made.

15.2 Analysis Sets

There shall be three analysis sets in this study. The Analysis Sets details will be provided in the statistical analysis plan before data base lock.

15.2.1 Safety Analysis Sets

The safety analysis set will include all patients enrolled in the study who receive study medication. This analysis set will be used for demographics, baseline characteristics and all safety analyses, including physical examination, vital signs determination, safety laboratory tests, IOP, and AE summaries.

15.2.2 Full Analysis Sets

The full analysis set will consist of all patients who are randomized according to IWRS- randomized treatment assignment and receive at least one dose of study product and have at least one post-baseline measurement. This will be the primary analysis set for safety and efficacy analyses.

15.2.3 Per Protocol Analysis Sets

The per protocol set (PPS) will consist of the subset of the full analyses set who do not meet criteria for per protocol set exclusion. These criteria are to capture relevant non-adherence to the protocol and will be defined in the statistical analysis plan. Further criteria may be defined in the statistical analysis plan. The PPS will be a secondary analysis set for safety and efficacy analyses. Select demographic and baseline characteristics may also be summarized for the PPS.

15.3 Demographics and Baseline Characteristics

15.3.1 Demographics

Demographics will include age, gender (male/female), race, eye color, ethnicity, height, BMI, and body weight and will be summarized using descriptive statistics. These will include number of patients, mean, standard deviation, minimum, median, and maximum for continuous endpoints, and frequency and percentage for categorical endpoints

15.3.2 Baseline Characteristics

Baseline characteristics are measured at Day 1 (predose). Medical history, ocular history, vital signs, prior and concomitant medications, existing disease, and medical conditions will be summarized by treatment group. A comprehensive medical eye examination will be conducted at Day 1 (predose). Visual acuity as measured by ETDRS protocol at distance will be recorded. Baseline signs and symptoms will be assessed including (tear osmolarity, TBUT, corneal staining, Schirmer's test, and IOP).

15.4 Evaluation of Safety

Safety parameters include physical and ocular examinations, vital signs, AEs, routine safety laboratory values (hematology, serum chemistry, and urinalysis), and slit lamp examinations.

Incidence and severity of clinical AEs will be summarized by group within System Organ Class, and within Preferred Term. The number and percent of patients with abnormal findings for complete and brief physical examinations, ocular examination, and will be presented by group and study day. The proportion of patients who experience AEs will be tabulated by group. Observed values and/or change from baseline in vital signs, safety laboratory, and ocular examinations data will be summarized by group and study day/time. Further details of the SAP will be covered in a separate document.

15.5 Evaluation of Pharmacokinetics

There are no pharmacokinetic assessments in this study.

15.6 Exploratory Evaluation of Pharmacodynamics

There are no pharmacodynamic measurements in this study.

16 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1 Study Monitoring

The Sponsor or its designee will conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. Cambium Medical Technologies, LLC monitors, or monitors designated by Cambium Medical Technologies, LLC, will conduct scheduled site visits to the investigational center for the purposes of monitoring the study.

Site initiation visit

In advance of study start, Cambium Medical Technologies, LLC will conduct a Site Initiation Visit to provide the Investigator(s) and their staff with a comprehensive overview of the protocol and study

procedures and to review mutual obligations and requirements of regulatory authorities. A regulatory file or binder containing required documentation will be kept at the site for reference and inspection.

In addition, the Investigator will provide the Sponsor, or its designee, with documentation of IRB approval of the Study Protocol and the Informed Consent prior to study initiation and IRB approval of any subsequent amendments to the protocol or revision to the Informed Consent. Before an investigational site can enter a patient into the study, the Sponsor or a designee will visit the investigational study site to:

- Determine the adequacy of the facilities;
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

Routine Monitoring Visits

Routine monitoring visits will be made to assure compliance with the study protocol and regulatory requirements, to review and verify the patient's eCRF by comparing with source documents, to ensure adequate records of clinical supplies are maintained, and to assess the continued suitability of the investigational site. During the routine monitoring visit, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that Investigational Product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts)
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

The Investigator will allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

Study Closeout Visit

On completion of the study, the monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to Cambium Medical Technologies, LLC. Study closeout activities are performed to confirm that the site Investigator's study obligations have been met and post study obligations are understood. Closeout activities verify that study procedures have been completed, data collected, and if relevant, study intervention is returned to the responsible party or prepared for destruction. During the study close out visit a monitor from the Sponsor or representative will contact the investigational site, to insure completeness of the following:

- Study Forms
- Study Files
- Clinical Supplies
- Laboratory Records
- Notifications and equipment removal
- Patient rights and notifications

16.2 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the Sponsor's audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor or its designee immediately if contacted by a regulatory agency about an inspection.

16.3 Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient ICF and recruitment materials must be maintained by the Investigator and made available for inspection.

During the course of the study, the Investigator, or designee, will provide the IRB for the Investigational Site with the following documents (and any subsequent amendment to the document), as follows:

- Study protocol;
- Investigator's brochure;
- Informed consent form;
- Protocol deviation/violation reports, if required;
- Progress reports, if required;
- Relevant curricula vitae; and
- Advertising specific to patient recruitment.

Additionally during the course of the study, the Investigator, or designee, will report to the IRB SAEs that were sent to Regulatory Authorities as an expedited report, as well as any additional SAEs that may be required according to the IRB's policy.

17 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

17.1 Data Quality Control

Periodic on-site review of communications between the Investigator and investigational site study monitors, and review of eCRF data and source documents are the responsibility of the Sponsor, or designee. The eCRF data for each patient will be reviewed against source documents at the study sites by the investigational site study monitor.

The Investigator and investigational site will allow study related quality control monitoring and audits, IRB review, and/or regulatory inspection and will cooperate in providing direct access to source data and documentation.

17.2 Data Management

Study data will be collected on source documents. The Investigator must maintain adequate and accurate source documents. These records should include detailed notes on:

- The medical history prior to the patient's involvement in the study;
- Date of informed consent;
- The basic identifying information that links the patient's medical record with the eCRFs;
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the;
- The medical condition during the patient's involvement in the study;
- All AEs;
- The patient's exposure to the study medication;
- The patient's exposure to any concomitant therapy;
- All relevant observations and data on the condition of the patient throughout the trial;
- Justification for all entries in the patient's eCRF.

Electronic CRFs will be used for this study. The eCRF is an electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study patient. Data are recorded from the source documents, directly onto the eCRF. The eCRFs will identify study patients with unique patient identifiers.

Data recording must follow the instructions described in the eCRF Completion Guidelines. The electronic data capture being used in this study will be TrialMaster (OmniComm Systems). The Principle Investigator (PI) has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The Principle Investigator (PI) or designee, as identified on Form FDA 1572, must electronically sign the completed eCRF for each participating patient to attest to their accuracy, authenticity, and completeness.

All personnel using the eCRF data entry system will be trained and the training documented. All changes to the database are recorded in an audit trail. The database will be locked when all outstanding queries have been addressed, all agreed to data is marked as source verified, and the PI has signed off on the eCRF contents.

An eCRF is required and must be completed for each consenting and enrolled patient by qualified and authorized personnel. Patients who fail the Screening assessments will not have an eCRF. All data in the eCRF must reflect the corresponding source document. Any corrections to entries made on the eCRF must be documented in a valid audit trail. Only data required by the protocol for the purposes of the study should be collected within the electronic data capture system.

The eCRFs will be processed at Medelis (Nashville, TN) Electronic CRF data items will undergo quality control standards of operation and be compliant with 21CFR part 11. Unresolved errors, omissions, or requests for clarification will trigger a query to the Investigational Site for resolution via electronic queries. The database will be corrected for completeness and accuracy. Prior and concomitant medications will be entered into the eCRF and coded using the World Health Organization Drug Reference List (WHO-DRL). Medical history, concurrent medical conditions, and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A quality assurance audit will be conducted to verify the accuracy and completeness of the database and will be done prior to declaring database lock. The database will not be altered after lock, unless joint written agreement is obtained between the CRO and the Sponsor.

18 ETHICS

18.1 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or Independent Ethics Committee (IEC) as appropriate prior to commencement of study related procedures at the site. The Investigator must submit written approval to the Sponsor or its designee before he/she can enroll any patient into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the Investigational Product. The Sponsor or its designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

18.2 Ethical Conduct of the Study

The conduct of this study will be consistent with ICH Guidance E6, GCP, and U.S. Federal regulatory requirements, as applicable. This study will be conducted in accordance with the principles of protection of healthy human patients participating in clinical medical research that have their origin in the Declaration of Helsinki.

18.3 Written Informed Consent

Informed Consent of clinical study patients will adhere to the standards set forth by the ICH-GCP guidance. The written ICF must be reviewed and approved by the Sponsor prior to submission to the Investigational Sites' IRB. The IRB must approve the written ICF prior to the initiation of the study.

The ICF will be used to explain to the patient the risks and benefits of study participation in simple terms (**Appendix 21.14**). The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients will be notified that they are free to discontinue from the study at any time and allowed time to consider the information provided.

The Investigator is responsible for ensuring that Informed Consent is obtained from each patient and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol-specific procedures. The Informed Consent discussion will allow the Investigator, or designee, opportunities to answer patient's questions about the study. One copy of the signed written ICF will be given to the patient and the original, signed copy will be retained by the Investigator.

19 STUDY CONDUCT AND RECORDKEEPING

19.1 Retention of Records

The Investigator must retain a copy of all study documents in accordance with the FDA or local regulations, whichever are the more stringent.

A searchable offline version of the eCRFs will be forwarded to the Sponsor for storage upon completion of the study. A copy of each completed eCRF will remain in the Investigator's study file on a compact disk. All source documentation, eCRFs, and administrative records will be retained by the Investigator:

- For a minimum of two years following the date the new marketing application (NDA) is approved for the indication for which the drug was investigated for;
- For a minimum of two years following the release date of the final report, if no marketing application is to be filed, or if the marketing application is not approved for the indication of which the drug was investigated or is discontinued and the FDA has been notified; or,
- For a minimum of 15 years after the completion or discontinuation of the study to be filed in support of the registration in the European Union.

After this time, the documentation will either be destroyed or transferred to the Sponsor or designee.

If the Investigator relocates, retires, or withdraws from the study for any reason, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or the Sponsor. No study documentation should be destroyed or moved to a new location without prior written approval by the Sponsor.

19.2 Data Collection

For all written documentation such as source documents, the data collected during the study must be legibly printed using a permanent ink pen. A single line should be drawn through any incorrect information. Opaque correction fluids or tapes are not permitted. All corrections or deletions to any of the source documents must be dated and initialed. All corrections or deletions to the eCRF will be documented via an electronic audit trail. The Investigator will electronically sign each patient's final eCRF to signify that all of the information is correct and complete.

19.3 Publication Policy

Study findings are an integral part of the overall commercialization plan for this investigational compound. The publication plan of the Sponsor, considering proprietary patent issues and competitive strategic goals, must be considered prior to the public disclosure of any aspect of this study by abstract, verbal presentation, invited lecture, journal article, or journal letter. No study information may be publicly

disclosed without the review and written consent of the Sponsor. Matters regarding authorship and the order of authorship on publications reporting the results of single study findings are covered in a separate agreement.

19.4 Protocol Amendments

Minimally, any change that significantly affects the safety of patients will be effected by means of a protocol amendment approved by the Sponsor. Any changes that affect patient safety or welfare must be submitted to the relevant IRB and approved before implementation.

The Investigator will provide written agreement of the protocol amendment via the approval signature page. The Investigator will notify the IRB of the amendment and obtain approval prior to implementation. If the change is intended to eliminate an immediate hazard, the amendment will be implemented immediately, prior to IRB notification.

19.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, FDA, or IRB requirements. Should a deviation from the protocol be deemed crucial for the safety and wellbeing of a particular trial patient, such a deviation will be instituted for that patient only. The Investigator or other attending physician should contact the Medical Monitor as soon as possible. In addition, the Investigator or designee should document in the source document the reasons for the protocol deviation and the ensuing events.

The noncompliance may also be on the part of the Investigator or the study site staff. As a result of these deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- Compliance with Protocol,
- Quality Assurance and Quality Control
- Noncompliance

It is the responsibility of the site to use continuous vigilance to identify and report deviations as soon as possible after occurrence and identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the Sponsor and to the data Management group.

The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

Serious noncompliance on the part of the site, and an inability of the Sponsor to bring the site back into compliance, will be reported to the FDA in accordance with their requirements.

19.6 Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. This insurance will cover all parties involved in the trial including, but not necessarily limited to, the Principal Investigator, clinical trial site, and patients. The Sponsor's insurance does not relieve the Investigator or the collaborators of any obligation to maintain their own liability insurance policy as required by the applicable law.

19.7 Confidentiality

All study findings and documents will be regarded as confidential. The Investigators and members of their research teams must not disclose such information without prior written approval from the Sponsor or its representatives.

The anonymity of participating patients must be maintained. A Protected Health Information statement will be provided to each patient either as a part of the Informed Consent document or as a separate form. Patients will be identified on eCRFs and other documents by their initials, birth date, and patient number. Documents that identify the patient by name (e.g., the signed ICF) must be maintained in strict confidence by the Investigators.

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21 APPENDICES

21.1 Ocular Examinations

The medical eye examination consists of an evaluation of the physiological function and the anatomical status of the eye, visual system, and its related structures. This will include the elements shown in **Table 9**. In addition, for the purpose of this study, corneal staining with fluorescein and conjunctival staining with lissamine green will be performed at selected visits. All measurements are to be recorded on the source document and in the eCRF. Some qualitative measures and ratings will be recorded as normal or abnormal. If an abnormal finding is discovered, the Investigator will determine whether the finding is clinically significant (CS) or not clinically significant (NCS). Any clinically significant change after dosing will be recorded on the AE page of the eCRF.

Table 9. Adult Eye Examination Assessments

Assessment	Observation	Evaluation
Visual acuity	BCVA will be recorded on Days 1, 21, and 42, as total letter score using the ETDRS protocol (see **Appendix 21.11**) in each eye following refraction.	ETDRS letter count converted to logMAR for mathematical calculations
External examination	• Iris pigmentation to be determined grossly as: Black, Blue, Brown, Hazel, Green, Grey, Other (to be specified); and indicated as a number 1-24 • Interpretation: 1-3 grey; 4-6 blue, 7-9 green, 10-12 hazel, 13-15 light brown, 16-18 brown, 19-21 dark brown, 22-24 black (see **Appendix 21.9**) • Eyelid position and character, lashes, lacrimal apparatus and tear function; globe position; and pertinent facial features • Ocular signs of irritation as indicated by redness or injection in the bulbar conjunctiva; indicated on a scale of 1-10 and rated as normal or abnormal (CS or not CS) (see **Appendix 21.10**)	Black, Blue, Brown, Hazel Green, Grey, Other and Color 1-24 Normal or Abnormal (CS, not CS) Range number 1-10
Ocular Discomfort (VAS)	Patients will be asked questions **about their current ocular discomfort** by indicating from 0 (no discomfort) to 100 (maximal discomfort)	Range number 0-100

Assessment	Observation	Evaluation
OSDI	The OSDI is assessed on a scale of 1-100 with higher scores representing greater disability The OSDI questionnaire includes total, visual-related function, and trigger subscales The Index is determined by multiplying the sum of the scores from each question by 25 and dividing the product by the number of questions answered. A continuum of scores from normal to dry has been developed	Range number 0-100
Symptom Frequency Rating (VAS)	A Symptom frequency scale to evaluate the frequency of 8 **symptoms at the time of each visit**. The patient will be asked to rate the frequency of their symptoms since the last visit by indicating from 0 (Never) to 100 (Constant): • Burning stinging • Itching • Foreign body sensation • Eye discomfort • Eye dryness • Grittiness • Photophobia • Pain	Range number 0-100
Tear osmolarity	Tear osmolarity will be measured using the TearLab® osmometer using the Eseries instrument or comparable The mean of two measures (2 in each eye will be calculated) taken at least 2 minutes apart will be recorded Investigators will perform tear osmolarity tests at screening, at Day 1 predose (baseline), Day 21, and Day 42. Tests will be conducted during the open label crossover at Day 70 and Day 91. Tear osmolarity will be recorded in integrals of 275- 400 mOsm/L Tear osmolarity from both eyes will be recorded in the source document and a single mean will be calculated Interpretation of osmolarity as: normal (under 300), mild (301-320), moderately abnormal (320-340), severely abnormal (>340); **or undetectable**	Range number (275-400 mOsm/L) or **undetectable**

<table>
<tr><th>Assessment</th><th>Observation</th><th>Evaluation</th></tr>
<tr><td>Slit-lamp microscopic examination</td><td>

Eyelid margins and lashes; tear film; conjunctiva; sclera; cornea; anterior chamber (AC);
Iris, lens, and anterior vitreous, prior to dilation.
Assess extent of anterior cells and flare certain visits

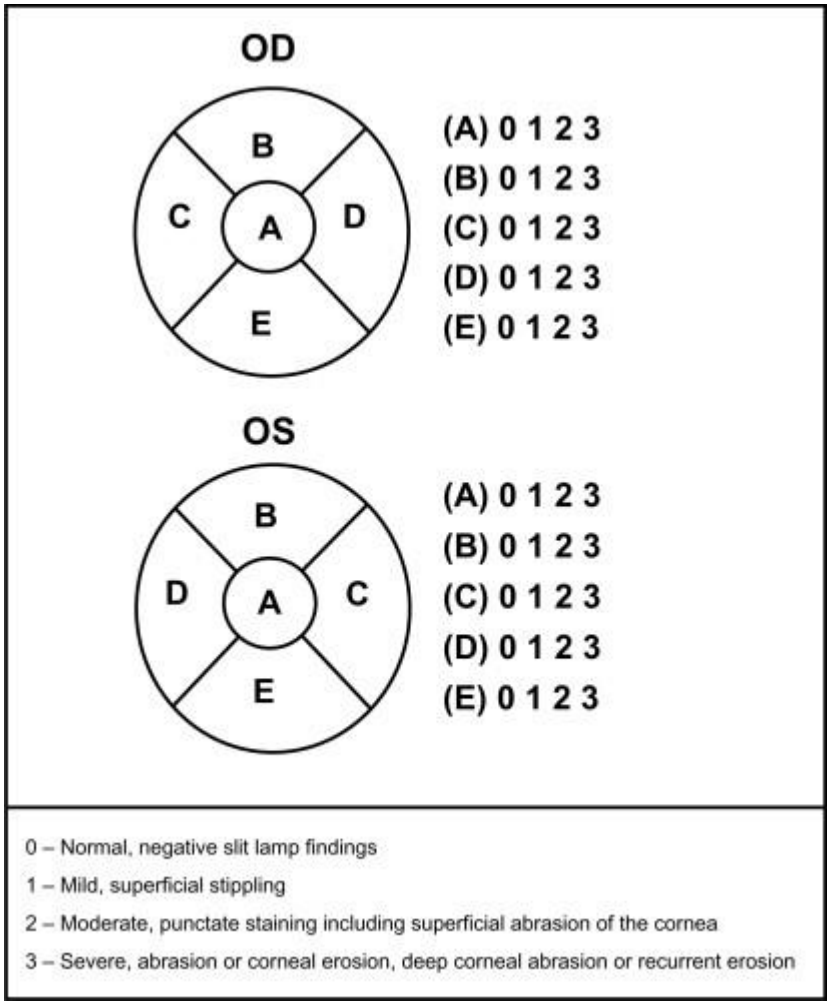
<table>
<tr><th>Grade</th><th>Aqueous Cells</th><th>Global evaluation</th></tr>
<tr><td>0</td><td>None</td><td>Normal</td></tr>
<tr><td>Trace</td><td>1-5 cells seen in 45 seconds or 1 minute</td><td rowspan="5">Abnormal
(CS/NCS)

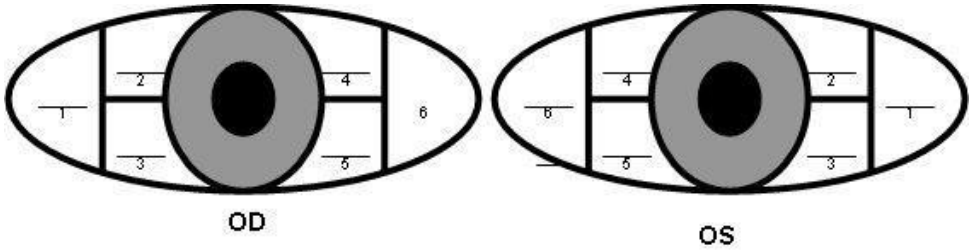
For an abnormal case, the investigator will determine whether it is clinically significant or not.</td></tr>
<tr><td>1+</td><td>6-15 cells seen at once</td></tr>
<tr><td>2+</td><td>16-25 cells scattered throughout beam</td></tr>
<tr><td>3+</td><td>26-50 (Dense scattering of cells; too many to count)</td></tr>
<tr><td>4+</td><td>> 50 or hypopyon</td></tr>
<tr><th>Grade</th><th>Flare (Slit Beam)</th><th>Global evaluation</th></tr>
<tr><td>0</td><td>Optically empty, compared bilaterally</td><td>Normal</td></tr>
<tr><td>1+</td><td>Faint haze (any appreciable light in slit beam) or not equal bilaterally</td><td rowspan="4">Abnormal
CS/NCS

For an abnormal case, the investigator will determine whether it is clinically significant or not.</td></tr>
<tr><td>2+</td><td>Mild: but iris details are clear through slit beam</td></tr>
<tr><td>3+</td><td>Moderate: iris and lens details hazy</td></tr>
<tr><td>4+</td><td>Severe dense haze: obvious plasmoid aqueous or fibrin present in anterior chamber</td></tr>
</table>
</td><td>Normal

Abnormal
(CS, NCS)</td></tr>
</table>

Assessment	Observation	Evaluation
Tear break up (TBUT)	Tear break up time will be recorded for each eye: • The mean of 3 measures will be calculated • Investigators will perform tear break up tests at screening, at Day 1 predose (baseline), Day 21, and Day 42. Tests will be conducted during the open label crossover at Day 70 and Day 91 • Break up time will be recorded in source/ document and eCRF as integers of 0-20 secs • Below 5 seconds indicates unstable tear film • Above 10 seconds indicates a normal, stable tear film	Range time (0-20 secs) Normal Abnormal (break up time less than 5±2 seconds) If abnormal, CS or NCS □

Assessment	Observation	Evaluation
Corneal staining (fluorescein)	Fluorescein staining of the corneal epithelium will be performed in both eyes following determination of TBUT. Fluorescein Dye will be placed in the eye using a micropipette or commercially obtained paper impregnated with fluorescein dye moistened with a full single drop (must be at least 10 µL) of balanced salt solution (BSS). Cobalt blue light will be used to illuminate the cornea The patient will be asked to blink several times in order to disperse the dye uniformly. The cornea will be examined 4-8 minutes after instillation using the cobalt blue filter in each of 5 zones on a scale of 0-3 **Figure 3. Corneal staining scale and zones**  Corneal staining will be graded using the Oxford grading system according to A J Bron anthony.bron@eye.ox.ac.uk. See **Appendix 21.12**	Total score for 5 regions: (A) Central, (B) superior, (C) nasal, (D) temporal, (E) inferior On a scale of 0-3. Maximum score for 1 eye is 15

Conjunctival staining (lissamine green)	• Conjunctival staining will be performed in both eyes by instilling 1 (approx. 10 µl) drop of 1% Lissamine green solution, performing a slit lamp examination, and scoring the amount of staining • Visibility of staining may be enhanced using a white light source and a red barrier filter, to give a black pattern on a red ground. A suitable filter is a Hoya 25A, or a Kodak Wratten 92 • Conjunctival staining will be graded using the Oxford grading system according to A J Bron anthony.bron@eye.ox.ac.uk. See **Appendix 21.12** • Only the temporal and nasal zones will be graded; the corneal region will not be graded. See **section 21.12** **Figure 4. Conjuctival staning zones**  	*Grade: 0, I, II, III, IV, V for 3 6 regions indicated OD and OS :
Schirmer test	• The Schirmer test will be performed as one of the last tests (in order to avoid producing artefactual staining of the cornea or conjunctiva) in both eyes with anesthesia for all study visits. • Amount of wetting from tears will be averaged between OD and OS and measured in mm • Two drops of topical anesthetic will be instilled OU 2 minutes before insertion of the Schirmer strips. • The eye should be lightly blotted with tissue to remove excess anesthetic or tears. The filter paper strips will be placed at the junction of the middle and lateral 1/3 of the lower eyelid, avoiding contact with the cornea. • Strips should be placed in both eyes at the same time and remain in place for 5 minutes. The patient may sit with his/her eyes gently closed during this period and should avoid excessive blinking during the test. • Amount of wetting will be recorded in millimeters (mm). Wetting of less than 5 mm is indicative of deficient tear production	Range (0-20 mm) Interpretation Normal Abnormal (7 ± 2 mm or less)

<table>
<tr><th>Assessment</th><th>Observation</th><th>Evaluation</th></tr>
<tr><td>Intraocular pressure measurement</td><td>• Preferably with a contact applanation method (typically a Goldmann tonometer)
• IOP measurements will be performed with calibrated Goldmann applanation tonometers or other standard devices as long as the same device is used every time
• Baseline IOP: The baseline IOP is defined as the pressure obtained on Day 1 (predose) and prior to initiation of Treatment. Each IOP is reported as the mean of three (3) measures.</td><td>Mean IOP, of 3 measures, OS and OD
Range
10-30 mmHg</td></tr>
<tr><td>Dilated Fundus examination; indirect ophthalmoscopy examination</td><td>• Mid and posterior vitreous, retina (including posterior pole and periphery), vasculature, and evaluation of optic nerve using mydriatic drops and accessory diagnostic lenses</td><td>Normal
Abnormal (CS, NCS)</td></tr>
<tr><td>Investigators Global Assessment</td><td><table><tr><th>Score</th><th>Grade</th><th>Definition</th></tr><tr><td>0</td><td>Complete improvement</td><td>All signs and symptoms of disease have resolved</td></tr><tr><td>1</td><td>Excellent improvement</td><td>Nearly all signs and symptoms have resolved. Only minimal symptoms and signs remain</td></tr><tr><td>2</td><td>Marked improvement</td><td>Majority of signs and symptoms have resolved</td></tr><tr><td>3</td><td>Moderate improvement</td><td>Significant improvement but many signs and symptoms remain</td></tr><tr><td>4</td><td>Minimal improvement</td><td>Slight overall improvement but not clinically significant</td></tr><tr><td>5</td><td>No change</td><td>Overall severity similar to baseline</td></tr><tr><td>6</td><td>Worse</td><td>Worse than baseline</td></tr></table></td><td>Range
0-6</td></tr>
</table>

Note: ETDRS = Early Treatment Diabetic Retinopathy Study; OS = oculus sinister (left eye); OD = oculus dexter (right eye); IOP = intraocular pressure, CS = clinical significant, NCS = not clinically significant.

21.2 Visual Analogue Scale for Ocular Discomfort and Frequency of Symptoms

Ask the following Question: On a scale of 1-100; indicate the frequency of your <u>current</u> symptoms.

Table 10. Visual Analogue Scale (0-100) Frequency of Ocular Symptoms

	0----------50----------100 Never Constant									
Burning stinging										
Itching										
Foreign body										
Eye discomfort										
Eye dryness										
Photophobia										
Pain										
Other____										

Patients will select a block corresponding from 0 (never)-100 (constant) on this scale to answer question **about the frequency of their symptoms.**

Ask the following Question: On a scale of 1-100; in terms of discomfort indicate your <u>current</u> feeling about your eyes.

Table 11. Visual Analogue Scale (0-100) Ocular Discomfort

	0----------50----------100 No Discomfort Intense Discomfort									
Eye discomfort										

Patients will select a block corresponding from 0 (no discomfort)-100 (intense discomfort) on this scale to answer the question **about their current ocular discomfort.**

21.3 OSDI Index

Table 12. OSDI Questions

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

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

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

Subtotal score for answers 1 to 5 (A)

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

Subtotal score for answers 6 to 9 (B)

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

Subtotal score for answers 10 to 12 (C)

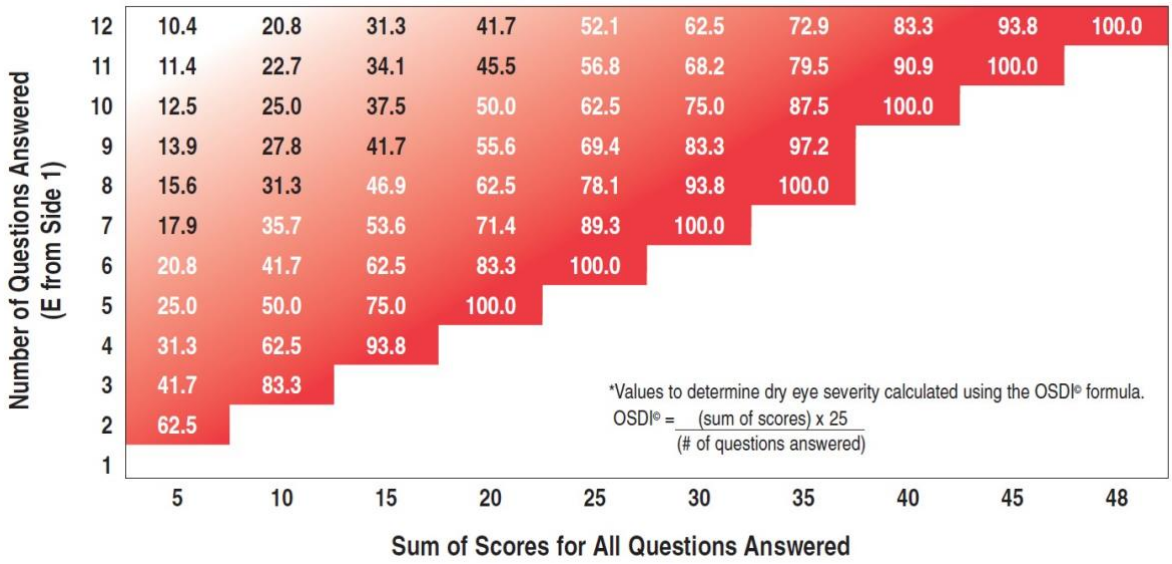
Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

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

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

21.3.1 Calculation and Continuum of Dry Eye scores for OSDI

Figure 5: Calculations for OSDI



21.4 Tear Osmolarity

TearLab® Osmolarity Testing:
Electronic Check Card-Quality Test
Perform only once per day of study patient testing. Following the TearLab® instruction guide, test each Pen with the Electronic Check Card. Record the test results in the TearLab® QC Log. If the test result is not within the expected range listed in the Electronic Check Card instructions, **do NOT test study patients** and contact Sponsor immediately.

When testing the control solution or the electronic check cards, make sure the results match the expected values shown in the instruction sheets. If they do not match, the quality tests have failed and testing should be stopped. Contact TearLab customer support in your area or call TearLab at (858) 455-6006.

Osmolarity Control Solutions
Always test each box of cards when received via mail using one card per box tested with the high control to ensure there is no damage from shipping. Record and date on QC form. Perform only once per day of study patient testing, following the TearLab® instruction guide, test the appropriate level control solution as shown. Each control solution ampoule should be used only once and discarded.

Record the test results in the TearLab® QC Log. If the test results are not within the expected range listed in the Control Solution instructions, repeat testing using high control. Follow provided protocol for repeat QC testing prior to contacting TearLab Customer Service.

Osmolarity Tear Testing

- Tear Testing must precede all other diagnostic examinations, testing and staining, except for Visual Acuity.
- **Patient must refrain from administrating any tear supplements within two hours** prior to the tear osmolarity test.
- Following the TearLab instruction guide, test the right eye and the left eye of the study patient.
- Record all results on the Case Report Form.

21.5 Washout of Prohibited Medications and Drugs

Patients must refrain from recreational consumption of marijuana in any form from 21 days before first dose until 7 days after the last dose.

Contact lenses wear use should be discontinued 14 days prior to Day 0 and should not be used during the duration of the study.

Use or suspected use of prohibited medications at Day 1 will be grounds for dismissal from the study.

21.6 Record of Alcohol, Tobacco and Marijuana Use

Tobacco and recreational marijuana are not to be used during this trial.

The consumption of alcoholic drinks in moderation is permitted. Moderation is defined as one drink a day for females and two drinks a day for men. One drink is defined as 12-ounces of beer, a five-ounce glass of wine and 1.5 ounces of spirits.

The Investigator will inquire about of alcoholic drinks, tobacco, and marijuana at the screening, 21, and 42-day exam.

Table 13. Sample Question for Alcoholic Drinks, Tobacco, and Marijuana Use

Over the past 2 weeks, how much alcohol do you estimate that you have consumed in the past week: ☐ 0 drinks ☐ 1-2 drinks ☐ 2-4 drinks ☐ 4-6 drinks ☐ 6-8 drinks ☐ 8-10 drinks ☐ >10 drinks In the same 2 weeks, what type of alcoholic drink did you consume most often? ☐ None ☐ Beer ☐ Wine ☐ Spirits
Over the past 2 weeks, how many cigarettes or tobacco products do you estimate that you smoked or used? ☐ None ☐ 1-2 cigarettes ☐ 2-14 cigarettes ☐ >14 cigarettes

Over the past 2 weeks, did you use any marijuana? ☐ yes ☐ no
If yes, was the marijuana prescribed by a licensed practitioner? ☐ yes ☐ no

21.7 Drug Labeling

Labels

It should be noted that the pharmacist is unmasked when dispensing study drug (**Section 10.6.2**).

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

Primary label:

- Protocol number
- Investigational new drug statement
- Lot number
- Storage conditions
- Name and address of the Sponsor **Figure 6: Investigative Product Label** Planned 32-pack container label:

CAM-101 Lot # xxxxxxx
(1 mL/dropper bottle)
For topical administration

Contains no preservatives

Store frozen in home freezer at or below 0° Fahrenheit
(–20 ± 3o Centigrade)

Manufactured for Cambium Medical Technologies, LLC

1055 Brookhaven Walk NE
Atlanta, GA 30319-4569

"**Caution: New Product –Limited by Federal law for Investigational Use"**

Planned bottle label or stamp:

CAM-101
Lot # xxxxxxx

21.8 Proper Instillation of Eye Drop

Installation of eye drop in the eye

Thaw the bottle over night before use in the refrigerator or for **60 minutes** at room temperature 1) Wash hands.

2) Remove the cap from eye drop bottle and inspect the cap to make sure that it is not cracked of damaged. Place cap on its side. Do not touch the tip of the eye dropper

3) Tilt head back and look up. Try focusing on something. Keep the eyes wide open.

4) Put 1 or 2 fingers on the face, just below the eye. Gently pull down to create space between the lower eyelid and the surface of the eye

5) With the other hand, bring the bottle close to the eye and point the tip towards the eye. Be careful not to touch the eyelashes or the surface of the eye with the tip of the bottle.

6) Squeeze bottle gently to instill one drop into the lower lid. Repeat if the drop misses the eye.

7) Remove fingers from face. Gently close lids. Tilt the head down.

8) Try not to blink for a few seconds, allowing drop to spread evenly over the eye,

9) Repeat step 3-8 for the second eye, using the same bottle.

10) Return cap to bottle. Place the used bottle in the container cup.

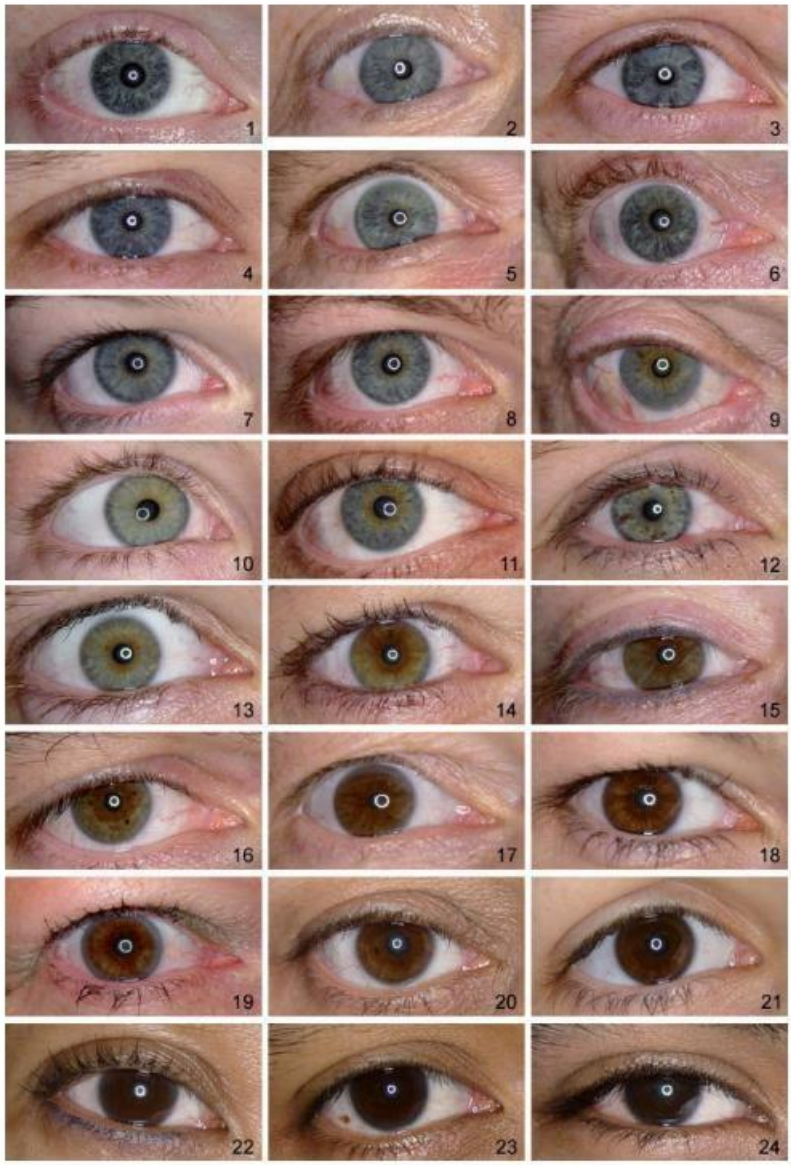
11) Use a new bottle for the next dose of the day,

12) When all 4 doses have been taken, return the 4 used bottles to the carton. Insert them upside down in the appropriate slot in the carton.

13) Check the appropriate box in the patient diary whenever a dose has been taken.

21.9 External Eye Exam: Eye Color

Figure 7: Iris Color Chart

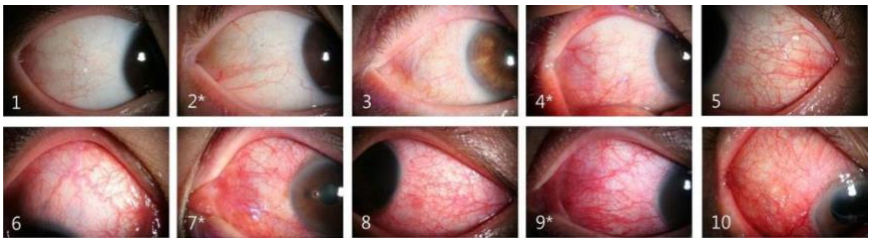


Reference set for classification of iris pigmentation. Source: (Franssen, Coppens et al. 2008, by permission)

Eye color will be assessed as part of the external eye exam at predose (Day –1), Visits 2 and 3 (Days 21 and 42) and at Follow-up. The same lighting condition at each visit to be used when evaluating healthy patient eye color. Match the patient's eye color with the image that best approximates it. Record the Number of the eye color on the source document.
Interpretation: 1-3 grey; 4-6 blue, 7-9 green, 10-12 hazel, 13-15 light brown, 16-18 brown, 19-21 dark brown, 22-24 black.

21.10 External Eye Exam: Redness or Injection in the Bulbar Conjunctiva

Figure 8. Color Scale Injection Bulbar Conjunctiva



Source: Park K et al., New Clinical Grading Scales and Objective Measurement for Conjunctival Injection. *Invest. Ophthalmol. Vis. Sci.* 2013;54(8):5249-5257.

Representative photographs of standard images of conjunctival injection from grade 1 to 10 (**Figure 8**).

Select grade that matches patient's eyes and record the number in the source document. If Grade is ≥3, the Investigator must also indicate whether the redness is normal or abnormal. If abnormal then the Investigator must indicate whether the finding is clinically significant or not clinically significant.

Table 14. Grading of bulbar conjunctival redness

Grade	Observation	Global evaluation
1-2	White and quiet	Normal
3-4	Slight, usually normal	Normal or Abnormal For an abnormal case, the investigator will determine whether it is clinically significant or not.
5-6	Mild	
7-8	Moderate	
9-10	Severe	

21.11 ETDRS BCVA Examination Chart

Figure 9. Sample ETDRS Chart

RIGHT EYE (OD)						Chart Line	LEFT EYE (OS)					
Chart 1 ETDRS					Number Correct	LogMar	Chart 2 ETDRS					Number Correct
N	C	Z	K	O		1.0	D	S	R	K	N	
R	H	S	D	K		0.9	C	K	Z	O	H	
D	O	V	H	R		0.8	O	N	R	K	D	
C	Z	R	H	S		0.7	K	Z	V	D	C	
O	N	H	R	C		0.6	V	S	H	Z	O	
D	K	S	N	V		0.5	H	D	K	C	R	
Z	S	O	K	N		0.4	C	S	R	H	N	
C	K	D	N	R		0.3	S	V	Z	D	K	
S	R	Z	K	D		0.2	N	C	V	O	Z	
H	Z	O	V	C		0.1	R	H	S	D	V	
N	V	D	O	K		0.0	S	N	R	O	H	
V	H	C	N	O		-0.1	O	D	H	K	R	
S	Z	H	C	Z		-0.2	Z	K	C	S	N	
O	Z	D	V	K		-0.3	C	R	H	D	V	
N = Total Number Correct							N = Total Number Correct					

[Source: http://precision-vision.com/product-category/etdrs-clinical-trial/etdrs-charts/original-series-etdrs-charts/]

Best Corrected Visual Acuity will be measured at Screening (Day –14 to 0), predose (Day 1), Follow-up and after dosing on each visit (Day 21 and Day 42). Patients must not wear contact lenses for 2 weeks before Day 1 and during the study. Determine manifest refraction without contact lenses.

To measure BCVA using the ETDRS protocol, use standardized ETDRS visual acuity charts [(Precision Vision, 944 First Avenue, La Salle, IL, 61301, 800-772-9211 (phone), and 800-2232224 (fax)], standardized lighting, test distance of 4 m, and trial frames.

Three (3) charts are available: ETDRS Chart R, 1, and 2.

- Test BCVA in the right eye using EDTRS Chart 1 first. Occlude the left eye

- Test BCVA in the left eye using EDTRS Chart 2. Occlude the right eye
- Retest BCVA in either eye with chart R

Testing at Distance

With the lens correction obtained by subjective refraction in the trial frame, the patient is asked to read ETDRS Visual Acuity Chart 1 from the top with the right eye. The patient starts at the top of the chart and begins to read down the chart. The patient reads down the chart until he or she reaches a row where a minimum of three letters on a line cannot be read. The patient is scored by how many letters could be correctly identified.

The examiner records each letter identified correctly by the patient as he or she reads the chart by circling the corresponding letter on the ETDRS score sheet (or study form). Letters read incorrectly, or for which no guesses are made, are not marked on this form. Each letter read correctly is scored as one point. The score for each line (including zero if no letters were read correctly on that line) and the total score for the eye are recorded on the form, as soon as the four-meter testing has been completed.

If the number of letters read correctly at four meters is less than twenty, the test should be repeated at one meter and both the four-meter and one-meter totals should be recorded on the ETDRS score sheet (or study form). Both eyes should be tested at four meters before the patient is moved up to the one-meter test distance. It is strongly advised that the total number of letters correctly read at four meters be calculated as soon as the four-meter testing has been concluded in order to identify patients who require one-meter testing.

Calculating the Visual Acuity Score

If twenty or more letters are read correctly at the four-meter test distance, the visual acuity score is equal to the number of letters (N) read correctly at four meters +30. If one or more but less than twenty letters are read correctly at four-meter distance, the visual acuity score is equal to the number of letters read correctly at four meters plus the number of letters read correctly at one meter in the first six lines.

 If no letters are read correctly at either the four-meter distance or the one-meter distance, the visual acuity score is 0.

A decrease of ≥15 letters from baseline will be considered an AE

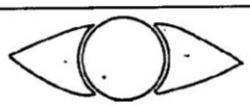
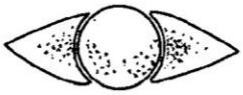
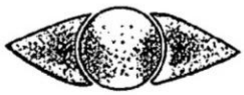
Table 15. Example Calculation of LogMar

Letter Score	LogMar	Snellen Equivalent
0-3	1.70-1.64	<20/800

4 to 8	1.62-1.54	20/800
9 to 13	1.52-1.44	20/640
14 to 18	1.42-1.34	20/500
19 to 23	1.32-1.24	20/400
24 to 28	1.22-1.14	20/320
29 to 33	1.12-1.04	20/250
34 to 38	1.02-0.94	20/200
39 to 43	0.92-0.84	20/160
44 to 48	0.82-0.74	20/125
49 to 53	0.72-0.64	20/100
54 to 58	0.62-0.54	20/80
59 to 63	0.52-0.44	20/63
64 to 68	0.42-0.34	20/50
69 to 73	0.32-0.24	20/40
74 to 78	0.22-0.14	20/32
79 to 83	0.12-0.04	20/25
84 to 88	0.02- -0.06	20/20
89 to 93	-0.08 to –0.16	20/16
94 to 97	-0.18 to –0.24	20/12

21.12 Oxford Grading Scheme for Conjunctival Staining

Figure 10. Oxford Grading Scheme for Conjunctival Staining

PANEL	GRADE	CRITERIA
A 	0	EQUAL TO OR LESS THAN PANEL A
B 	I	EQUAL TO OR LESS THAN PANEL B, GREATER THAN A
C 	II	EQUAL TO OR LESS THAN PANEL C, GREATER THAN B
D 	III	EQUAL TO OR LESS THAN PANEL D, GREATER THAN C
E 	IV	EQUAL TO OR LESS THAN PANEL E, GREATER THAN D
>E	V	GREATER THAN PANEL E

Dyes used in Corneal and Conjunctival Staining Fluorescein sodium (Corneal Staining)

Instill approximately 2 µl of 2 % sterile fluorescein into each conjunctival sac with a micropipette (using a sterile tip). Larger volumes risk the possibility of inadequate dilution into the fluorescent range. Alternatively, a fluorescein-impregnated strip may be used. Add the fluorescein to a very dry eye. The staining pattern of cornea will be documented with the Oxford scale. The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm. A suggested filter pair for detection of fluorescein staining is a yellow, Kodak Wratten 12 barrier filter (transmitting above 495 nm) or an orange Wratten 15 filter (transmitting above 510 nm) in combination with a blue Wratten 47 or 47A exciter filter. The 47A shows greater transmittance than the Wratten 47 over the absorption range. The 'cobalt' filter of many slit-lamps is suitable to use with a Wratten 12 or 15 barrier.

Lissamine Green (Conjunctival staining)

Instill 10 µL of 1% lissamine green into the cul-de sac of eye. The staining pattern of the conjunctiva will be documented with the Oxford scale a red filter within 4 minutes of lissamine green instillation. Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0, I, II, III, IV, V for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale.

21.13 Transport, Storage and Handling of Study Product

Following the Run-in period, all study medications will be dispensed frozen, patients should plan on transporting the study products home and storing them in a freezer as soon as possible (ideally ≤2 hours). Situations which may cause the study medications to thaw prematurely should be avoided. To help keep the study product frozen during transport, study medication cartons will be dispensed in a single insulated tote bag that is provided by the Investigator.

Each tote bag will contain 3 cartons. Each carton will contain 1 week's supply of study product (4 doses or bottles/day for 7 days). An extra day's supply (4 bottles) is also provided in case an additional supply is needed before the next scheduled patient visit.

Upon arrival at home, the patient should store the study product in the freezer immediately. The study medications require little space (<1/3 of an ice cream carton).

Patients should store all study medications (used or unused) in their respective cartons in the freezer.

Figure 11. Carton Containing 7-day Supply of Investigational Study Product

Figure 12. Insulated Bag for Transport of Investigational Study Products

21.14 Informed Consent

This protocol requires the following basic elements for Informed Consent:

- A statement that the study involves research; an explanation of the purposes of the research and the expected duration of the patient's participation; a description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the patient;
- A description of any benefits to the patient or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient;
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained. Note: Regulatory agencies and the Sponsor/designee may inspect all records;
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and if so, what they consist of, or where further information may be obtained;
- An explanation of whom to contact for answers to pertinent questions about the research and research patients' rights and whom to contact or in the event of research related injury to the patient;
- A statement that participation in the study is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled;
- A statement that the Medical Monitor is authorized to review research records.

When appropriate, one or more of the following elements of information shall also be provided to each potential trial participant.

- A statement that any particular treatment or procedure may involve risks to the patient (or to the embryo or fetus, if the participant is or may become pregnant) which are currently unforeseeable;
- Anticipated circumstances under which the participant's participation may be terminated by the Investigator without regard to the patient's consent;

- Any additional costs to the participant that may result from participation in the research;
- The consequences of a participants' decision to withdraw from the study and the procedures for orderly termination of participation by the patient;
- A statement that significant new findings developed during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient;
- A description of the approximate number of participants in the study;
- A description of what protected health information may be disclosed, to whom it may be disclosed, and for what period of time this disclosure is allowable;
- A Protected Health Information (HIPAA) statement, unless such statement is provided to the patient in a separate form;
- If this qualifies as an "applicable clinical trial," a statement describing this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law.

21.15 Protocol Investigator's Signature Page

Investigator's Agreement Protocol CAM-101-01

I confirm that I have read this protocol, I understand it, and I will work according to this protocol the applicable ICH–GCP guidelines for, and the applicable laws and regulations of the country of the study site for which I am responsible. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Cambium Medical Technologies, LLC. I will promptly submit the protocol to the applicable ethical review board.

Instructions to the Investigator: Please SIGN and DATE 2 copies of this signature page and PRINT your name, title, name and location of the facility in which the study will be conducted on both copies. Return 1 of the completed, signed copies to Cambium Medical Technologies, LLC.

_____ _____

Signature of Investigator Date

_____

Investigator Name

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility

(City, State (if applicable), Country)