STATISTICAL ANALYSIS PLAN

AUTHOR(S):	Kalyan Ghosh
PROJECT MANAGER:	David Hiller
SAP VERSION:	Final 1.0
DATE OF SAP VERSION	23 Dec. 2019
SPONSOR:	Cambium Medical Technologies, LLC. 1055 Brookhaven Walk, NE Atlanta, GA 30319-4659
STUDY TITLE:	A Randomized Multicenter Double-Masked Placebo-Controlled Parallel Phase I/II Study to Determine the Safety and Exploratory Efficacy of Topical Fibrinogen-Depleted Human Platelet Lysate in Patients with Dry Eye Secondary to Grahft vs. Host Disease
PHASE OF STUDY:	Phase 1/2
PROTOCOL NUMBER:	CAM-101-01
PROTOCOL VERSION/DATE:	Protocol Original 1.0, 21 July, 2017 Amendment 0.4, 19 September, 2018

APPROVALS

Name and Title	Signature	Date
Terrence A. Walts President and CEO Cambium Medical Technologies LLC		
Kalyan Ghosh, Ph.D. Biostatistician Inference, Inc		Jan 4, 2020

TABLE OF CONTENTS

1. ABBREVIATIONS 5
2. INTRODUCTION 7
2.1. Responsibilities 7
2.2. Timing of Analyses 7
3. STUDY OBJECTIVES AND ENDPOINTS 8
3.1. Study Objectives 8
3.2. Endpoints 8
3.2.1. Primary Outcome Measures 8
3.2.2. Secondary Endpoints 8
3.2.3. Exploratory Endpoints 9
4. STUDY DESIGN 10
4.1. Sample Size Justification 11
4.2. Schedule of Assessments (SoA) 11
5. ANALYSIS SETS 16
6. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS 17
6.1. Key Definitions 17
6.2. Visit Windows and Time Points 17
6.3. Multiplicity Issues 17
6.4. Subgroup Analyses 17
6.5. Missing Data 17
7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS 19
7.1. Patient Disposition and Populations 19
7.2. Demographic and Baseline Characteristics 19
7.3. Medical History 19
7.4. Prior and Concomitant Medication 20
7.5. Dosing Compliance 20
7.6. Dosing Compliance 21
8. EFFICACY 22
9. SAFETY 23
9.1. Adverse Events 23
9.2. Clinical Laboratory Assessments 24

9.3. Vital Signs 24
9.4. Ocular Examination 24
9.5. Physical Examination 25
10. ANALYSIS CONVENTIONS 26
11. REFERENCES 28
12. TABLES, LISTINGS, AND FIGURES 29

1. ABBREVIATIONS

Abbreviation or Special Term	Explanation
AC	Anterior chamber
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ARVO	Association for Research in Vision and Ophthalmology
AST	Autologous serum tears
β-hCG	Beta-human chorionic gonadotropin
BCVA	Best-corrected visual acuity
BMI	Body mass index
BUN	Blood urea nitrogen
CK	Creatine kinase
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
GGT	Gamma-glutamyl transpeptidase
GMP	Good manufacturing practices
GRAS	Generally recognized as safe
gtt	Gutta (a single drop)
GvHD	Graft versus host disease
Hb	Hemoglobin
Hct	Hematocrit
HGF	Hepatocyte growth factor
HIPAA	Health insurance portability and accountability act
HPF	High-power field
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Abbreviation or Special Term	Explanation
INR	International Normalized Ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
IP	Investigational Product
IWRS	Interactive web-response system
LDH	Lactate dehydrogenase
LDPE	Low-density polyethylene (plastic)
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
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
PT	Prothrombin clotting time
QID	Four times a day
RBC	Red blood cell
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.
T-Bil	Total bilirubin
TBUT	Tear film break-up time
TGF-β1	Transforming growth factor beta-1
TID	Three times a day
TP	Total protein
ULN	Upper limit of normal
USA	United States of America
vol/vol %	volume/volume %
VA	Visual acuity
VAS	Visual analogue scale
WHO-DRL	World Health Organization Drug Reference List

2. INTRODUCTION

The purpose of this plan is to prospectively outline in detail the data derivations, statistical methods and presentations of data so that valid conclusions can be reached to address the study objectives outlined in the protocol.

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

2.1. Responsibilities

Inference, Inc will perform the statistical analyses for all clinical data collected. Inference, Inc is responsible for production and quality control of all tables, figures and listings.

2.2. Timing of Analyses

There will be 2 formal analyses performed for this study. The first analysis will be for the blinded part of the study. The second analysis will be based on data from the open-label part of the study. An additional ad hoc unblinded analysis may be performed for administrative reasons and planning of future trials. If such analysis is performed, adequate precaution will be taken to ensure that the subject recruitment and data cleaning are not influenced by the personnel performing such analysis.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objectives:

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.

Secondary Objectives:

The secondary objective is to evaluate 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.

3.2. Endpoints

3.2.1. 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

3.2.2. Secondary Endpoints

The secondary outcome measures are:

- Change from baseline in fluorescein corneal staining on Day 42
- Change from baseline in lissamine green corneal 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

3.2.3. Exploratory Endpoints

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

4. STUDY DESIGN

This is 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 for the first 42 days of dosing, followed by an open-label, active only, crossover phase for the second 42 days of dosing. The following figure shows the overall schema of the study design:

Schematic of Overall Study Design:

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

Upon establishing eligibility, all patients, except highly responsive patients identified after the 2-week vehicle run-in period (a maximum of 12, who may be assigned directly to the 30 vol/vol% treatment group – see below), will be randomized 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 therefore have a 66% chance of being randomized to receive FD hPL.

After the run-in period, patients will be dynamically allocated 1:1:1 by IWRS to receive FD hPL test (10 vol/vol % or 30 vol/vol %) or the vehicle control product based on a composite score for "Symptom Severity." The word "dynamically" is used to stress the use of stratification (blocking) by baseline severity score ("Symptom Severity"). This will ensure that each treatment group will have equivalent ranges of severity.

The composite "Symptom Severity" score at baseline for each subject will be determined by assessing the top score in each of 4 categories on Day 0, within 24 hours of the end of the run-in period.

- OSDI score —assessed on a scale of 0-100
- Ocular discomfort VAS score —assessed on a scale of 0-100
- Ocular symptom frequency—assessed on a scale of 0-100 for each of 8 symptoms (Burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, grittiness, photophobia, pain)
- Frequency of use artificial tear —assessed on a scale of 0-4 (where 0=no drops and 4=>6 drops/day)

The patient scores in the 4 categories will be normalized and summed to obtain an un-weighted raw score of 0-4. The unweighted raw score will be multiplied by 25 to obtain a composite score of 0-100. The range of severity as determined by the baseline composite severity score was determined *a priori* as

- Mild—composite score 0-33

- Moderate—composite score 34-66
- Severe—composite score of 67-100

Note that the baseline composite severity score is the only stratification factor used in the randomization of this study. Specifically, investigative site is not a stratification factor, and there is no attempt to balance the treatment groups within investigative sites.

A special population of patients who have a significant improvement, defined by the Investigator as having >50% overall improvement in "Symptom Severity", at the end of the run-in period may be assigned and not randomized to receive 30 vol/vol % FD hPL at the start of the study at the investigators' discretion. Unlike roll-over patient results, whose safety and efficacy results will be aggregated with results from patients originally randomized into the 30 vol/vol% core study group, only these patients' safety results will be aggregated with core study patients' results receiving this study product.

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. While these patients' safety and efficacy results from their second 42 day study will be tracked and reported as a distinct group, their results will also be aggregated with results from patients originally randomized into the 30 vol/vol% concentration group as part of the overall Study.

4.1. Sample Size Justification

Approximately 60 patients (~20 each per 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 across all sites.

The sample size chosen for this study was based upon practical considerations. No *a priori* statistical assumptions have been made.

4.2. Schedule of Assessments (SoA)

The following assessments will be performed in this study:

Table 1: Schedule for Screening, Pre-dose, and Day 1

Study Phase		**Screening and Run-in**		**Dosing and Evaluation**		
Visit number				1		
Day (Time)		Day –30 to Day –14	Day –14 to Day 0	Day 1 (Predose)	Day 1 (8:00 ± 2 hr.)	Day 1 (≥ 2 hr. 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 (best corrected visual acuity by Early Treatment Diabetic Retinopathy Study [ETDRS])	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 break up time (TBUT)[8]	X		X		
	Corneal fluorescein stain	X		X		
	Corneal lissamine green stain	X		X		
	Schirmer's test with anesthesia	X		X		
	IOP	X[9]		X[9]		
	Dilated fundus exam	X[10]				
	Investigators global evaluation					X
Urine Pregnancy test (females of childbearing capacity only)		X[11]		X[11]		
Plasma FSH		X				

Plasma FSH	X				
Alcohol and drug abuse questionnaire	X[12]				
Safety laboratory: [13]	X[13]				
Confirm medical history no HIV, HCV, HBV past 12 mos	X				
Randomization			X		
Dispense new artificial tears		X[14]		X	
Dispense Investigative Product				X	
Instill Investigative Product				X[15]	
Adverse event surveillance	X[16]		X	X[16]	X
Diary recording and review[17]		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 2: Schedule for Days 21-42 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 3: Schedule for Day 49

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.

5. ANALYSIS SETS

A patient will be defined as *screened* after the signature of the informed consent, regardless of the completion of all the screening procedures.

A patient will be defined as *eligible* if he/she meets all the inclusion/exclusion criteria. Otherwise he/she will be defined as a *screen failure*.

A patient will be defined as *randomized* in the study when he/she is assigned to a randomized treatment arm at the end of the 2-week washout period.

There shall be three analysis sets in this study:

Safety Analysis Set (SAS): The safety analysis set will include all randomized patients who at least one dose of 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. Patients in the SAS will be analyzed as treated.

Full Analysis Set (FAS): The full analysis set will consist of all randomized patients who receive at least one dose of study medication and have at least one post-baseline measurement. This will be the primary analysis set for the efficacy analyses. Patients in the FAS will be analyzed as randomized, following the Intention-to-Treat principle.

Per Protocol Set (PPS): All patients in the FAS population who fulfill the study protocol requirements without major protocol violations that may affect study results will be included in this set. The list of major protocol violations will be finalized before the unmasking of the data. The PPS will be a secondary analysis set for the efficacy analysis. Demographic and baseline characteristics may also be summarized for the PPS. Patients in the PPS will be analyzed as treated.

6. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

6.1. Key Definitions

The Study Day is the day relative to the day of study drug administration (Day 1).

Unless otherwise specified, Baseline is the last non-missing observation before the start of study treatments.

The treatment period is defined as Days 1-42 for those patients dosed with any study treatment for the double-masked phase of the study; the follow-up period is defined as Days 46 to 52. For the cohort of subjects enrolled in the open-label phase, the treatment period is defined as Days 46-93.

6.2. Visit Windows and Time Points

There are no plans to derive visit windows, and visits will be used in the analyses as reported on the eCRF. Note that as per protocol, visits at Days 21, 42, 49, and 70 have a three-day window, and Day 91 has a two-day window.

6.3. Multiplicity Issues

For this early phase study, although two active dose groups and placebo are compared via a number of efficacy endpoints, and an administrative interim analysis may be performed, no multiplicity adjustment will be made since the treatment effect is only estimated in an exploratory fashion.

6.4. Subgroup Analyses

Due to the small size of this study, no inferential subgroup analyses are planned. Data will be summarized by baseline severity and identified as such in the corresponding listings. Data from the special population of 12 high responders in the placebo run-in period will be listed separately.

6.5. Missing Data

For the evaluation of the change from baseline in efficacy variables, data at baseline and Day 42 are required, but since the analysis is based on a repeated measures model it is not necessary that every patient has data on both visits. All patient data, complete or otherwise, will contribute to the analysis without any imputation for missing values. The repeated measures analysis with missing data is considered valid if the missing data is Missing At Random (MAR), that is, the probability of the data being missing does not depend on the unobserved missing data.

For prior and concomitant medication summaries, if the medication start date is completely missing then the medication will be considered to be both prior and concomitant unless it can be determined that the medication end date occurred prior to the study drug administration. If the medication start date is partially missing and the partial date is not sufficient to determine if the medication was taken after treatment administration then the medication will be considered to be both prior and concomitant for the study unless the partial date is clearly after the date of treatment administration (in which case it will be considered concomitant only) or the medication end date is prior to treatment administration (in which case it is prior only).

Completely missing or partially missing adverse event onset dates will be imputed as follows in case due diligence to obtain accurate adverse event information fails:

If the adverse event start date is completely missing then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to administration of study medication. If this is the case, the adverse event will not be considered treatment emergent.

If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the administration of study medication, then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to the start of the study. In the unlikely event of a missing laboratory result, the result will be treated as missing for the laboratory summary.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

7.1. Patient Disposition and Populations

Summary tables for patient disposition will be presented for all screened patients by treatment group. The patient disposition summary will contain the numbers of patients who signed informed consent, failed screening, were randomized, completed the blinded treatment period, and discontinued during the treatment period.

The primary reason for premature discontinuation during the treatment period will be summarized by treatment group for the SAS. Summary tables presenting the reasons for exclusion from the SAS will be provided for the randomized patients.

Number of patients included in specific analysis population will also be displayed.

Listings will be presented on patient disposition and protocol violations.

7.2. Demographic and Baseline Characteristics

All patients in the SAS will be used to summarize the demographic and baseline characteristics with respect to sex, age at entry into study, eye color, height, weight, BMI, race and ethnicity for each treatment group.

Continuous variables such as age, height, weight, and BMI will be summarized with descriptive statistics: n, mean, standard deviation, median, minimum and maximum value. The number and percent of each sex, eye color, race, and ethnicity category will be presented using counts and percentages.

A similar summary will be presented for the FAS.

The baseline severity score will be summarized for each of the four criterion and the composite score with descriptive statistics: n, mean, standard deviation, median, minimum and maximum value. Additionally, the counts and percentages for the composite score categories will be presented. This will be done for both the SAS and the FAS.

Other baseline characteristics as measured at Day 1 (pre-dose) such as vital signs will be summarized by treatment group for the SAS. Results from the comprehensive medical eye examination conducted at Day 1 (pre-dose) such as visual acuity (as measured by ETDRS), and other baseline signs and symptoms including tear osmolarity, TBUT, corneal staining, Schirmer's test, and IOP will also be summarized.

7.3. Medical History

Medical and surgical history including ocular history and existing diseases will be coded according to the latest version of the MedDRA dictionary. Frequency tables of the number and percentage of patients by system organ class and preferred term by treatment group will be provided for the SAS only.

7.4. Prior and Concomitant Medication

Medications will be separated into prior and concomitant medications. Prior medications are those with start and stop date before the date of start of study treatment. Medications taken after start of study medication and before stop of study medication, or medications which started before start of study medication but are ongoing after the start will be considered as concomitant.

Medications will be coded according to the latest version of the WHO Drug Dictionary. Listings will present the Anatomical Therapeutic Chemical classification system (ATC) Class Level 2, Class Level 3, generic name and the investigator term.

Prior medication and concomitant medication will be summarized for the Safety set. Frequency tables of the number and percentage of patients by ATC Class Level 2 and ATC Class Level 3 will be provided.

7.5. Dosing Compliance

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received (based on subject self-reporting in the subject diary) and comparing that to the number of expected doses as follows:

$$Compliance\ (\%) = \frac{Number\ of\ actual\ doses\ received}{Number\ of\ expected\ doses} \text{ x } 100\%$$

The number of actual doses received will be calculated from the number of expected doses – the number missed doses recorded in the eCRF and determined through review of the subject diary.

Days with unrecorded dosing in the subject diary will be considered to have missed doses.

The number of expected doses that will be used for calculating compliance will be calculated as

4 x [(date of last dose – date of Visit 1 [Day 1])]

for all subjects, regardless of study completion status. If a subject is lost to follow up and the date of last dose is unknown, the later of the last diary date and the last visit date will be used as the date of the last dose.

Significant investigational product or study procedure non-compliance is defined, per the protocol, as <80% or >120% of expected dose as determined by number of empty bottles returned and patient diary. A categorial dosing compliance variable will be derived based on this definition.

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group, using the SAS. The compliance categories defined above will be summarized with proportion of subjects in each category.

A subject listing of dosing compliance will also be produced.

7.6. Dosing Compliance

Extent of study drug exposure for all subjects will be calculated in days using the following:
Extent of Study Drug Exposure (days) = (Date of last study drop instillation – Date of Visit 1 [Day 1]) +1.
If a subject is lost to follow-up and the date of the last dose is unknown, the later of the last diary date or the last visit date will be used as the date of the last dose.
Extent of study drug exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group, using the SAS.

A subject listing of study drug exposure will also be produced.

8. EFFICACY

The efficacy analyses will primarily be performed on the FAS and considered exploratory in this study. Sensitivity analyses may be performed on the PPS in order to understand the robustness of the treatment effect.

While efficacy data will be collected and reported for the overall study, the efficacy data from the subpopulation of highly responsive patients, who are not randomized, will not be included in the efficacy analysis.

For efficacy endpoints where measurements from both eyes are available, a single mean will be calculated for the analyses. Left and right eyes may be analyzed separately as a secondary analysis.

For continuous endpoints, change from baseline will be summarized with descriptive statistics for the values at baseline, values at the time point (say, Day 21 and Day 42), and for change from baseline at the time point for the set of patients who have data at both the baseline and the time point being assessed. Percent change from baseline may also be summarized in a similar manner.

There are four secondary endpoints of interest in this study:

- Change from baseline in fluorescein corneal staining on Day 42
- Change from baseline in lissamine green corneal 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

There are also three exploratory endpoints of interest in this study:

- 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

For the analysis of the above efficacy endpoints, two-sided 95% confidence intervals will be presented for the difference in mean change from baseline between the active doses and the vehicle control. These confidence intervals will be based on a repeated measures model with treatment group, baseline severity category, visit and treatment-by-visit as fixed factors. The modelling will be done using the PROC MIXED procedure of the SAS® software. The correlation among the measurements across visits will be assumed to be unstructured, and a Kenward-Roger option for calculating the denominator degrees of freedom will be used.

If the data seem too skewed to justify the use of a parametric approach, a non-parametric approach (e.g. Hodges-Lehman) may be employed to calculate the 95% confidence interval for the difference in location.

Categorical endpoints, if explored, will be summarized using the patient count and percentage in each category with 95% confidence intervals calculated using the Wald method. No hypothesis testing will be conducted in this study.

9. SAFETY

Safety analyses will be performed on the SAS. Safety parameters include physical and ocular examinations, vital signs, AEs, routine safety laboratory values (hematology, serum chemistry, and urinalysis), and slit lamp examinations. Safety data will be reported for all patients including the special population patients, and patients in the open-label crossover phase following completion of the extension study.

The safety data from the subpopulation of highly responsive patients, though they are not randomized, will be included in the safety analysis.

9.1. Adverse Events

Adverse Events will be coded according to the latest version of the MedDRA dictionary.

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.

Adverse events shall be recorded starting at signing of ICF. AEs will be defined as treatment-emergent adverse events (TEAE), if they occurred after initiation of study treatment or if they started prior to study treatment but worsened after initiation of study treatment, given that worsening started within the treatment period or 30 days after last dose of study medication. All AEs will be listed and flagged as treatment emergent or non-treatment emergent.

Only TEAEs shall be summarized by treatment group in the clinical study report. Other AEs will be included in the medical history and will be listed in patient listings.

An overall summary with number and percentage of patients with all different TEAE categories, like treatment-related, serious, leading to withdrawal, and fatal will be provided by treatment group. A similar summary of the number and percentage of patients with ocular adverse events will be presented as well.

Incidence and severity of TEAEs will be summarized by treatment group within System Organ Class (SOC), and within Preferred Term (PT). The number and percent of patients with abnormal findings for physical examinations and ocular examinations will be presented by treatment group and visit.

TEAEs will also be summarized by relationship and by study period per SOC and PT. Relationships will be categorized into related (includes “Possible”, “Probable” and “Very Likely”) and unrelated (includes “Non-Related” and “Unlikely”).

Serious TEAEs, and TEAEs leading to discontinuation will be summarised by treatment with the number and percentage of patients with treatment emergent adverse events classified by system organ class and preferred term within system organ class. Serious s may also be summarized by relationship per SOC and PT.

All TEAEs, including Serious TEAEs, treatment-related TEAEs, TEAEs leading to discontinuation of the treatment, and discontinuation from study, will also be listed.

9.2. Clinical Laboratory Assessments

All patients in the Safety Analysis population who have a baseline laboratory assessment and at least one post-baseline assessment will be included in the presentation of the laboratory data. Note that only patients with SAEs are expected to have post-baseline laboratory results, as per the protocol. All laboratory evaluations, including those that are unscheduled, will be presented in the listings.

Clinical laboratory parameters including hematology, chemistry and urinalyses will be summarized by treatment group and visit. In addition, changes from the baseline visit will be calculated for each visit if baseline and post-baseline measurements are available.

Shift tables may also be used to display the change from before treatment to after treatment measurement with respect to the reference ranges "missing", "low", "normal", "high", and "total".

9.3. Vital Signs

All patients in the Safety Analysis population who have baseline vital signs assessments and at least one post-baseline assessment will be included in the presentation of the vital signs data. All assessments, including those that are unscheduled, will be presented in the listings.

Vital signs, including the assessments of systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate, will be summarized by treatment group and visit. In addition, changes from the baseline visit will be calculated for each visit.

9.4. Ocular Examination

The following ocular exams are performed pre-dose and at Days 1, 21, 42, 70, and 91.

- Frequency of artificial tear and IP use
- Visual acuity (best corrected visual acuity by Early Treatment Diabetic Retinopathy Study [ETDRS])
- External eye exam (ocular signs and symptoms)
- Ocular Discomfort (VAS)
- OSDI
- Symptom frequency rating (VAS)
- Tear osmolarity
- Slit lamp biomicroscopic exam
- Tear break up time (TBUT)
- Corneal fluorescein stain
- Corneal lissamine green stain
- Schirmer's test with anesthesia

- IOP
- Dilated fundus exam
- Investigators global evaluation

Descriptive statistics for the above exams will be summarized by treatment and visit. The number of patients in each treatment group that show a change from Normal to Abnormal with clinical significance in any ocular examination assessment at Day 42 may be presented in corresponding shift tables, where appropriate. Ocular exam results will also be listed.

9.5. Physical Examination

Physical exam will include general appearance, mood, and affect (mental status). Results will be listed.

10. ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS® program name, including the path that generates the output;
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all patients. Row entries in tables are made only if data exists for at least one patient (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of patients (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no patient satisfied. The summary tables clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data.

Supportive individual Patient Data Listings will be sorted and presented by treatment, patient number, and visit date, if applicable.

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data are flagged in the individual patient data listings. Imputed data will not be incorporated into any raw or primary datasets. The imputed data will be retained in the derived / analysis datasets.

The total duration for a patient *on study* will be calculated as the difference between the date of initial exposure to the study drug and the last day of observation plus one day. All calculations for defining the duration on study will follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE – FIRST DOSING DATE + 1].

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%).

- All summary tables will include the analysis set sample size (i.e., number of patients).

- Study Day 1 is defined as the first day the patient is exposed to treatment. All *study days* are determined relative to the day of exposure to the treatment.

- Baseline values will be defined as those values recorded closest to, but prior to, the first study treatment on Day 1.

- Change from baseline will be calculated as follows:

  Change = Post-baseline value – baseline value.

- Date variables will be formatted as DD-MMM-YYYY for presentation.

- SAS® Version 9.3[1] or higher will be the statistical software package used for all data analyses.

- The study treatment, and patient number will be included in all data listings. All listings will be sorted by study treatment, baseline severity, patient number and visit date, as applicable.

11. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.

12. TABLES, LISTINGS, AND FIGURES

Tables, listings and figures will be listed in a separate Data Displays Document.

APPROVALS

Name and Title	Signature	Date
Terrence A. Walts President and CEO Cambium Medical Technologies LLC	Terrence A. Walts	1/5/20
Kalyan Ghosh, Ph.D. Biostatistician Inference, Inc		