CLINICAL TRIAL PROTOCOL: SDP-4-CS201

Study Title:	A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group, Dose-Response Study of SDP-4 Ophthalmic Solution in Subjects with Dry Eye Disease (DED)
Study Number:	SDP-4-CS201
Study Phase:	2
Product Name:	SDP-4 Ophthalmic Solution
Indication:	Dry eye disease
Investigators:	Multicenter
Sponsor:	Silk Technologies, Ltd.
Sponsor Contact:	Brian Lawrence, PhD
Medical Monitor:	Charles Slonim, MD

	Date
Original Protocol:	27 February 2019
Amendment 1:	03 April 2019

SYNOPSIS

Sponsor: Silk Technologies, Ltd.

Name of Finished Product: SDP-4 Ophthalmic Solution

Name of Active Ingredient: Silk-Derived Protein-4 (SDP-4)

Study Title:
A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group, Dose-Response Study of SDP-4 Ophthalmic Solution in Subjects with Dry Eye Disease (DED)

Study Number: SDP-4-CS201

Study Phase: 2

Primary Objective:
Assess the safety and efficacy of SDP-4 ophthalmic solution in subjects with DED over a 12-week (84-day) treatment period.

Study Design:
This is a Phase 2, multicenter, double-masked, randomized, vehicle-controlled, dose-response, parallel-group study designed to evaluate the ocular and systemic safety and efficacy of SDP-4 ophthalmic solution in subjects with moderate to severe DED in both eyes (OU) over a 12-week (84-day) treatment period.

Subjects will be randomized to 1 of 3 concentrations (0.1%, 1.0% and 3.0%) of SDP-4 Ophthalmic Solution or vehicle in a 1:1:1:1 ratio in parallel groups. All investigational product (SDP-4 concentrations and vehicle) will be provided in single-use doses (SUDs) contained in foil pouches. Subjects, the Investigator, and all site personnel responsible for performing study assessments will remain masked to treatment assignment.

Investigational product (IP) will be administered via topical ocular instillation, one drop per eye, twice daily (BID) for 12 weeks (84 days). Both eyes will be treated. A 2-week screening/run-in period on BID vehicle will precede the 12-week randomized treatment period.

Subjects must have a Symptom Assessment in Dry Eye (SANDE) total score of ≥ 40 at Visit 1/Screening and Visit 2/Day 1 to enter the trial. For subjects with a qualifying SANDE score who meet all other inclusion/exclusion criteria, the eye with the lower tear break-up time (TBUT) at Visit 2/Day 1 will be designated as the study eye. In the event both eyes have the same TBUT scores, the eye with the lower Schirmer's test score will be designated as the study eye. If both eyes have the same TBUT and Schirmer's test scores, the right eye will be designated as the study eye.

The study will consist of 7 clinic visits, 2 visits during the screening period and 5 on-treatment visits: Visit 1 (Day -14 ± 2/Screening Visit), followed by the 2-week run-in on BID vehicle, Visit 2 (Day 1/Confirmatory and Randomization Visit), Visit 3 (Day 7 ± 2), Visit 4 (Day 14 ± 2), Visit 5 (Day 28 ± 2), Visit 6 (Day 56 ± 4) and Visit 7 (Day 84 ± 4/End of Study Assessments).

If a subject complains of persistent dry eye symptoms, the site may provide the subject with unpreserved artificial tears (provided by the Sponsor), to be used only if necessary. The subject must return all used and unused artificial tears at each visit so the site can conduct accountability to assess the use of artificial tears. Artificial tears may not be used within 2 hours prior to any study visit.

Study Population:

Number of Subjects Planned:

A total of 300 randomized subjects are planned, with 75 subjects assigned to each dose group of SDP-4 Ophthalmic Solution (0.1%, 1.0% and 3.0%) or vehicle.

Inclusion Criteria:

Individuals must meet the following criteria at Screening (Visit 1/Day -14) **and** Visit 2/Day 1:

1. Willing and able to understand and sign an informed consent form prior to any study-related procedures.
2. Male or female patients 18 years of age or older.
3. Willing and able to follow study instructions, able to self-administer IP or have IP administered by a caregiver throughout the study period, and able to be present for the required study visits/assessments for the duration of the study.
4. Have DED in both eyes, as supported by a subject-reported history of daily symptoms of dry eye for ≥ 6 months prior to Visit 1/Screening.
5. Total score ≥ 40 on the SANDE questionnaire.
6. History of artificial tear use in the 30 days prior to Visit 1/Screening and willingness to discontinue use during the study.
7. Tear break-up time (TBUT) of ≤ 6 seconds in both eyes.
8. Anesthetized Schirmer's test tear volume ≥ 3 mm and <10 mm in both eyes.
9. Best-corrected visual acuity (BCVA) of +0.7 logMAR or better in each eye as assessed by logMAR chart.
10. Female patients must be 1 year postmenopausal, surgically sterilized, or females of childbearing potential with a negative urine pregnancy test at Visit 1/Screening and Visit 2/Day 1. Females of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.

Exclusion Criteria:

Ocular

1. Ocular surface corneal disease, other than DED.
2. Diagnosis of Sjögren's disease.
3. Lid margin disorder other than meibomian gland dysfunction (MGD) (e.g., active anterior blepharitis including staphylococcal, demodex or seborrheic; excessive lid laxity, floppy eyelid syndrome, ectropion, entropion) that in the Investigator's opinion could affect study parameters/assessments.
4. Presence of any ocular condition (e.g., pterygium) that in the Investigator's opinion could affect study parameters.
5. Any previous reconstructive or cosmetic eyelid surgery that may affect the normal function of the lids (e.g., blepharoplasty, ptosis repair, entropion/ectropion repair).
6. Any previous invasive glaucoma (e.g., trabeculectomy, shunt) and/or corneal surgery (e.g., penetrating keratoplasty, lamellar keratoplasty, Descemet's stripping endothelial keratoplasty [DSEK]).
7. Corneal refractive surgery (e.g., laser-assisted in situ keratomileusis [LASIK], photorefractive keratectomy [PRK], limbal relaxing incision [LRI]) within 12 months prior to Visit 1/Screening.
8. Cataract extraction, with or without minimally invasive glaucoma surgery (MIGS), within 90 days prior to Visit 1/Screening.
9. Cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal within 30 days prior to Visit 1/Screening or planned during the study. If a subject has a punctal plug at

Visit 1/Screening for ≥ 30 days and it falls out during the study, it should be replaced with a new plug of the same type.

Exclusion Criteria (continued):

Prior Medications

10. Contact lens wear.
11. Use of isotretinoin (Accutane®) within 60 days prior to Visit 1/Screening.
12. Use of topical cyclosporine (Restasis®, Cequa®) or topical lifitegrast (Xiidra®) within 45 days prior to Visit 1/Screening.
13. Use of any of the following medications within 30 days prior to Visit 1/Screening:
    - Topical ophthalmic corticosteroids or topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs)
    - Autologous serum
    - Topical ophthalmic antibiotics or antivirals
    - Topical ophthalmic antihistamines or mast cell stabilizers
    - Topical ophthalmic medications for lowering of intraocular pressure (IOP) for treatment of glaucoma or ocular hypertension
    - Systemic immunosuppressive agents
    - Systemic (i.e., oral, intravenous, intra-articular, intrathecal, epidural, or intramuscular) corticosteroids (intranasal, inhaled, dermatologic, or peri-anal steroids are allowed)
    - Tetracycline compounds (tetracycline, doxycycline or minocycline)

Current Medications

14. Any changes in the dosing of any chronically used systemic drug within 90 days prior to Visit 1/Screening and throughout the study period, including but not limited to the following:
    - Anticholinergics
    - Antidepressants including selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SSNRIs), tricyclics, and benzodiazepines
    - Antihistamines
    - Systemic H1-receptor antagonists
    - β-adrenoceptor antagonists
    - Calcium channel blockers
15. Any changes in the dosing of aspirin and aspirin-containing products within 30 days prior to Visit 1/Screening and throughout the study period.

General

16. Stevens-Johnson syndrome.
17. History of immunodeficiency disorder, HIV, positive hepatitis B, C, or evidence of acute active hepatitis A (anti–HAV IgM).
18. History of organ or bone marrow transplant.
19. History of graft versus host disease (GvHD).
20. Systemic lupus erythematosus.
21. Chronic pain syndrome (e.g., fibromyalgia).
22. Systemic signs of infection (e.g., fever or current treatment with antibiotics).

Exclusion Criteria:

General (continued):

23. Serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance, including, but not limited to, severe cardiopulmonary disease, uncontrolled hypertension, and/or uncontrolled diabetes.
24. Known history of alcohol and/or drug abuse within 12 months prior to Visit 1/Screening that, in the opinion of the Investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject.
25. Known allergy or contraindication to any component of IP formulation or diagnostic agents.
26. Participation in any drug or device clinical investigation within 30 days prior to Visit 1/Screening and/or during the period of study participation.
27. Screening and enrollment of more than one individual who resides in the same household at the same time (participation is allowed after the other individual has been determined to be a screen failure or after the other individual has completed Visit 7/Day 84).
28. Screening and enrollment of employees of the clinical site.

Investigational Product, Dose, and Mode of Administration:

SDP-4 Ophthalmic Solution (0.1%, 1.0% and 3.0%), 1 drop in each eye BID

Reference Therapy, Dosage and Mode of Administration:

Vehicle, 1 drop in each eye BID

Duration of Treatment:

Twelve (12) weeks (84 days)

Efficacy Assessments:

Symptoms

- SANDE
- Rating on visual analogue scale (0-100 mm) of individual symptoms:
  - Itching
  - Foreign body sensation
  - Burning/stinging
  - Fluctuating vision
  - Eye dryness
  - Eye discomfort
  - Photophobia
  - Eye pain

Signs

- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Conjunctival hyperemia
- Anesthetized Schirmer's test

Safety Assessments:

- Ocular and non-ocular adverse event (AE) monitoring
- BCVA
- Biomicroscopy
- IP comfort assessment
- Dilated fundus exam
- IOP measurement

Criteria for Evaluation:

Primary Efficacy Endpoint

- Mean change from baseline in total SANDE score at Visit 7/Day 84

Secondary Efficacy Endpoints

- Mean and mean change from baseline at each visit for each of the following evaluations:
  - Conjunctival lissamine green staining (combined and each zone)
  - Corneal fluorescein staining (combined and each zone)
  - TBUT
  - Anesthetized Schirmer's test
  - Conjunctival hyperemia
  - Individual symptom VAS scores, separately for each symptom
- SANDE
  - Mean change from baseline in total SANDE score at each visit
  - Mean total SANDE score at each visit
  - Mean and mean change from baseline in each component of SANDE at each visit

Statistical Methods:

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock.

General Considerations

All continuous study assessments will be summarized by treatment and visit (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

All study data will be listed by treatment, subject, and visit (as applicable).

The unit of analysis for efficacy will be the study eye.

Sample Size Rationale

A sample size of 70 subjects per treatment group will have 80% power to detect a treatment difference of 11.7 units in SANDE total score and 1.2 seconds in TBUT at 12 weeks using a t-test with a 0.05 two-sided significance level. Over-enrollment of 5 subjects per group/20 subjects per study is planned to account for discontinuations.

Statistical Methods (continued):

Analysis Populations

The intent-to-treat (ITT) population will include all randomized subjects who received IP.

The per protocol (PP) population is a subset of the ITT population, which will include all subjects who complete the study without major protocol deviations.

The safety population will include all subjects who received IP.

Table 1 Schedule of Visits and Examinations

	Visit 1 Day -14 ± 2 Screening	Visit 2 Day 1 Randomization	Visit 3 Day 7 ± 2 Treatment	Visit 4 Day 14 ± 2 Treatment	Visit 5 Day 28 ± 2 Treatment	Visit 6 Day 56 ± 4 Treatment	Visit 7 Day 84 ± 4 End of Treatment
Informed consent	X						
Review inclusion/exclusion criteria	X	X					
Demographics	X						
Medical and ocular history	X						
Concomitant medication/review	X	X	X	X	X	X	X
Urine pregnancy test	X	X					X
SANDE	X	X	X	X	X	X	X
VAS assessment of individual symptoms		X	X	X	X	X	X
IP comfort assessment		X	X	X	X	X	X
Best-corrected visual acuity	X	X	X	X	X	X	X
Biomicroscopy and external eye exam	X	X	X	X	X	X	X
Tear break-up time	X	X	X	X	X	X	X
Corneal fluorescein staining by zone	X	X	X	X	X	X	X
Conjunctival lissamine green staining by zone	X	X	X	X	X	X	X
Anesthetized Schirmer‘s test	X	X					X
Intraocular pressure measurement	X				X		X
Dilated fundus exam	X						X
Dispense run-in medication/instruction on run-in administration/evaluate administration	X						
Randomization		X					
Dispense investigational product (IP)/instruction on IP administration		X			X	X	
Dispense artificial tears[a]	X	X	X	X	X	X	

	Visit 1 Day -14 ± 2 Screening	Visit 2 Day 1 Randomization	Visit 3 Day 7 ± 2 Treatment	Visit 4 Day 14 ± 2 Treatment	Visit 5 Day 28 ± 2 Treatment	Visit 6 Day 56 ± 4 Treatment	Visit 7 Day 84 ± 4 End of Treatment
Adverse event assessment	X	X	X	X	X	X	X
Run-in medication/IP/artificial tear accountability (if applicable)[a]		X	X	X	X	X	X

IP = investigational product; SANDE = Symptom Assessment in Dry Eye; VAS = visual analogue scale

[a] If a subject complains of persistent dry eye symptoms, the site may provide the subject with unpreserved artificial tears (provided by the Sponsor), to be used only if necessary. The subject must return all used and unused artificial tears at each visit so the site can conduct accountability to assess the use of artificial tears. Artificial tears may not be used within 2 hours prior to any study visit; the subject may either be rescheduled or may wait at the site until 2 hours have passed since instillation if this occurs.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ANOVA	Analysis of variance
BCVA	Best-corrected visual acuity
BID	Twice daily
CFR	Code of Federal Regulations
CRA	Clinical research associate
DED	Dry eye disease
DSEK	Descemet's stripping endothelial keratoplasty
eCRF	Electronic case report form
eDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCLE	Human corneal limbal epithelial (cells)
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IL	Interleukin
IND	Investigational New Drug
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
ITT	Intent-to-treat
LASIK	Laser-assisted in situ keratomileusis
LLOQ	Lower limit of quantification
LRI	Limbal relaxing incision

MedDRA	Medical Dictionary for Regulatory Activities
MIGS	Minimally invasive glaucoma surgery
MMP	Matrix metalloprotease
MW	Molecular weight
NF-κB	Nuclear factor κB
NSAID	Non-steroidal anti-inflammatory drug
OHT	Ocular hypertension
OU	Both eyes
PP	Per protocol
PRK	Photorefractive keratectomy
SAE	Serious adverse event
SANDE	Symptom Assessment in Dry Eye
SDP-4	Silk-derived protein-4
SOP	Standard operating procedure
SSNRI	Selective serotonin norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
SUD	Single-use dose
TEAE	Treatment-emergent adverse event
TBUT	Tear break-up time
TNF-α	Tumor necrosis factor-alpha
US	United States

1. INTRODUCTION

Silk-derived protein-4 (SDP-4) is a novel biotherapeutic being developed by Silk Technologies, Ltd. (Silk Technologies) as a treatment for the signs and symptoms of dry eye disease (DED). Dry eye disease, as defined by the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II, is a "multifactorial disease of the ocular surface characterized by 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" (Craig et al., 2017).

The disease results in corneal irregularities that can create sight-limiting outcomes over time due to chronic inflammation governed by nuclear factor κB (NF-κB) signaling, which is thought to play a significant role in disease pathogenesis (Lan et al., 2012). Inflammatory mediators regulated by NF-κB, such as matrix metalloprotease (MMP)-9, tumor necrosis factor alpha (TNF-α), and interleukin (IL)-8 have been found in the tear fluid at high concentrations in patients exhibiting severe DED (Solomon et al., 2001; Smith et al., 2001). Furthermore, topical administration of MMP-9 to DED MMP-9-knockout mice subjected to dry eye via cholinergic blockade significantly increases corneal epithelial permeability, implicating MMP-9 in increased corneal epithelial disruption and damage (Pflugfelder et al., 2005). Collectively, these observations suggest a relationship between disruption of the corneal epithelium, increased secretion of MMP-9 through NF-κB signaling, and the signs and symptoms of DED.

Silk fibroin protein is the primary fibrous component of the *Bombyx mori* silkworm cocoon. *In vivo*, aqueous silk fibroin protein solution was successfully used to treat DED in a murine animal model, improving clinical outcomes (increased tear production, decreased corneal irregularity, inhibited epithelial cell detachment, and increased goblet cell density) and reducing inflammatory cytokine presence (intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1, MMP-2 and MMP-9) (Kim et al, 2017).

Silk-derived protein (SDP) is a partially hydrolyzed population derived from the silk fiber protein fibroin with a molecular weight (MW) distribution of 2000–300, 000 Daltons (Da). *In vitro* studies in immortalized hCLE cells subjected to scratch wound denudement demonstrated that aqueous SDP improved corneal epithelial wound healing through accelerated cell migration, proliferation and enhanced cell-matrix attachment (Abdel-Naby et al., 2017). Cultures treated with SDP displayed significant increases in cell-matrix focal adhesion formation and basement membrane adhesive strength compared to untreated cultures. *In vivo*, treatment with SDP accelerated the acute healing phase of injured rabbit corneal epithelial tissues, as shown by significantly increased epithelial migration rate, and produced a dose-dependent, 8-fold decrease in MMP-9.

Through a series of additional manufacturing steps, the subpopulation, SDP-4, is produced with a MW range of 10,000-30,000 Da. In nonclinical studies, SDP-4 has demonstrated a dual mechanism of action that both inhibits inflammation and physically improves the stability of the tear film. SDP-4 inhibits NF-κB driven expression of known dry eye inflammatory mediators produced by ocular surface cells, including MMP-9, TNF-α, and IL-8.

Multiple *in vitro* assays revealed that SDP-4 inhibits NF-κB-driven expression of known dry eye inflammatory mediators produced by the corneal epithelium. SDP-4 treatment inhibited secretion of IL-8 by stimulated hCLE cells in a dose-dependent manner. Treatment with SDP-4 also impaired chemokine activation and subsequent mobilization of immune-like cells in an *in vitro* co-culture model. Direct impairment of NF-κB activity by SDP-4 was confirmed using a human embryonic kidney cell line containing a NF-κB-responsive reporter gene. SDP-4 inhibited reporter gene expression dose dependently at concentrations ranging from 0.1%-10%.

Cardiovascular and respiratory safety pharmacology studies were conducted in the monkey and rat, respectively, with SDP-4 administered by intravenous (IV) injection. No statistically significant effects on respiratory rate, tidal volume or minute volume or on cardiovascular function, e.g., electrocardiographic waveforms, QT, heart rate, were observed at doses of 0, 10, 50 and 75 mg/kg.

The pivotal 90-day toxicity study in rabbits was conducted at SDP-4 concentrations of 0% (vehicle), 1%, 3%, 5% or 10% instilled four times/day into both eyes. Ocular findings in all groups, including controls, occurred sporadically throughout the dosing phase with no relationship to dose or duration of treatment. Irritation observed during the study tended to resolve during the dosing phase as the study progressed. No histopathological changes in the ocular tissue were observed. Plasma levels of SDP-4 were either below the lower limit of quantification (LLOQ) or approximated the LLOQ at the highest dose. Based on the results, the no observed adverse effect level (NOAEL) for this study was 10%, the highest dose examined.

A pivotal 28-day IV toxicity study in rats was undertaken at doses of 0, 10, 50 and 75 mg/kg. No SDP-4-related toxicity was observed. Microscopically, dose-related cytoplasmic vacuolation was noted in the proximal convoluted tubule segment of the renal nephron, which was reduced in severity following the 14-day recovery phase but not completely resolved. Because there were no other histopathological changes observed in the kidney and no clear evidence of altered renal function at any dose, the finding is considered to have limited toxicological significance. A dose proportional increase in plasma levels of SDP-4 was observed. The half-life was approximately 0.5-1 hr and no accumulation of SDP-4 was evident.

The pharmacological and toxicological data for SDP-4 are considered adequate to support the safe clinical use of the SDP-4 drug product for the initial Phase 2 clinical trial. Based on the results of the toxicology program, the estimated margin of safety on a body surface area basis was determined to be 128-fold. Therefore, ocular instillation of SDP-4 twice daily to patients with a maximum clinical concentration of 3% administered twice daily for up to 12 weeks is considered safe for the initial Phase 2 clinical study.

SDP-4 Ophthalmic Solution is a topical treatment for DED that has not been evaluated in clinical trials. The planned first in human (FIH) study is a multicenter, double-masked, randomized, vehicle-controlled, dose-response, parallel-group study designed to evaluate the ocular and systemic safety and efficacy of SDP-4 in subjects with moderate to severe DED in both eyes over a 12-week (84-day) treatment period. For additional information regarding SDP-4 Ophthalmic Solution, please refer to the Investigator's Brochure (IB).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to assess the safety and efficacy of SDP-4 Ophthalmic Solution in subjects with DED over a 12-week (84-day) treatment period.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2, multicenter, double-masked, randomized, vehicle-controlled, dose-response, parallel-group study designed to evaluate the ocular and systemic safety and efficacy of SDP-4 ophthalmic solution in subjects with moderate to severe DED in both eyes (OU) over a 12-week (84-day) treatment period.

Subjects will be randomized to 1 of 3 concentrations (0.1%, 1.0% and 3.0%) of SDP-4 Ophthalmic Solution or vehicle in a 1:1:1:1 ratio in parallel groups. All investigational product (IP) (SDP-4 concentrations and vehicle) will be provided in single-use dose (SUD) containers seal packed into foil pouches. Subjects, the Investigator, and all site personnel responsible for performing study assessments will remain masked to treatment assignment.

The IP will be administered via topical ocular instillation, one drop per eye, twice daily (BID) for 12 weeks (84 days). Both eyes will be treated. A 2-week screening/run-in period on BID vehicle will precede the 12-week randomized treatment period.

Subjects must have a Symptom Assessment in Dry Eye (SANDE) total score of ≥ 40 at Visit 1/Screening and Visit 2/Day 1 to enter the trial. For subjects with a qualifying SANDE score who meet all other inclusion/exclusion criteria, the eye with the lower tear break-up time (TBUT) at Visit 2/Day 1 will be designated as the study eye. In the event both eyes have the same TBUT scores, the eye with the lower Schirmer's test score will be designated as the study eye. If both eyes have the same TBUT and Schirmer's test scores, the right eye will be designated as the study eye.

The study will consist of 7 clinic visits, 2 visits during the screening period and 5 on-treatment visits: Visit 1 (Day -14 ± 2/Screening Visit), followed by the 2-week run-in period on BID vehicle, Visit 2 (Day 1/Confirmatory and Randomization Visit), Visit 3 (Day 7 ± 2), Visit 4 (Day 14 ± 2), Visit 5 (Day 28 ± 2), Visit 6 (Day 56 ± 4) and Visit 7 (Day 84 ± 4/End of Study Assessments).

If a subject complains of persistent dry eye symptoms, the site may provide the subject with unpreserved artificial tears (provided by the Sponsor), to be used only if necessary. The subject must return all used and unused artificial tears at each visit so the site can conduct accountability to assess the use of artificial tears. Artificial tears may not be used within 2 hours prior to any study visit.

See Table 1, Schedule of Visits and Examinations.

3.2. Rationale for Study Design and Control Group

It is hypothesized that by reducing pro-inflammatory mediators of DED, and providing a mucin replacement to enhance spreading and wetting of the tear film, SDP-4 may produce improvement in the symptoms of DED, as measured by the total SANDE score, and in the physical characteristics of the tear film, as measured by TBUT. These are designated primary (SANDE) and secondary (TBUT) endpoints. The study is also designed to measure additional secondary endpoints including individual symptoms (itching, foreign body sensation, burning/stinging, fluctuating vision, eye dryness, eye discomfort, photophobia, and

eye pain) and additional signs (anesthetized Schirmer's test, corneal fluorescein staining, conjunctival lissamine green staining, and conjunctival hyperemia). Three concentrations of SDP-4, (0.1%, 1.0% and 3.0%) will be dosed topically BID versus vehicle control to test the hypotheses of this protocol. The SDP-4 concentrations are among those shown in nonclinical pharmacology studies to be effective in inhibiting inflammatory mediators, with the 1% concentration producing maximal inhibition of NF-κB activity. The 12-week (84-day) treatment period allows adequate assessment of the comparative efficacy of the IP concentrations being compared and their effects over time. The control is the vehicle without the active ingredient of the drug product to be used in the study.

3.3. Study Duration and Dates

The duration of study treatment is 12 weeks (84 days). The overall duration of the study is 14 weeks, which includes a 2-week screening/run-in period on vehicle and 12 weeks of treatment.

4. STUDY POPULATION SELECTION

4.1. Study Population

A total of 300 randomized subjects with DED (see Section 4.2) are planned, with 75 subjects assigned to each dose group of SDP-4 Ophthalmic Solution (0.1%, 1.0% and 3.0%) or vehicle.

4.2. Inclusion Criteria

Individuals must meet the following criteria at Screening (Visit 1/Day -14) and Visit 2/Day 1:

1. Willing and able to understand and sign an informed consent form prior to any study-related procedures.
2. Male or female patients 18 years of age or older.
3. Willing and able to follow study instructions, able to self-administer IP or have IP administered by a caregiver throughout the study period, and able to be present for the required study visits/assessments for the duration of the study.
4. Have DED in both eyes, as supported by a subject-reported history of daily symptoms of dry eye for ≥ 6 months prior to Visit 1/Screening.
5. Total score ≥ 40 on the Symptom Assessment in Dry Eye (SANDE) questionnaire.
6. History of artificial tear use in the 30 days prior to Visit 1/Screening and willingness to discontinue use during the study.
7. Tear break-up time (TBUT) of ≤ 6 seconds in both eyes.
8. Anesthetized Schirmer's test tear volume ≥ 3 mm and <10 mm in both eyes.
9. Best-corrected visual acuity (BCVA) of +0.7 logMAR or better in each eye as assessed by logMAR chart.
10. Female patients must be 1 year postmenopausal, surgically sterilized, or females of childbearing potential with a negative urine pregnancy test at Visit 1/Screening. Females of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.

4.3. Exclusion Criteria

Individuals who meet any of the following criteria will be excluded from the study.

Ocular

1. Ocular surface corneal disease, other than DED.
2. Diagnosis of Sjögren's disease.

3. Lid margin disorder other than meibomian gland dysfunction (MGD) (e.g., active anterior blepharitis including staphylococcal, demodex or seborrheic; excessive lid laxity, floppy eyelid syndrome, ectropion, entropion) that in the Investigator's opinion could affect study parameters/assessments.
4. Presence of any ocular condition (e.g., pterygium) that in the Investigator's opinion could affect study parameters.
5. Any previous reconstructive or cosmetic eyelid surgery that may affect the normal function of the lids (e.g., blepharoplasty, ptosis repair, entropion/ectropion repair).
6. Any previous invasive glaucoma (e.g., trabeculectomy, shunt) and/or corneal surgery (e.g., penetrating keratoplasty, lamellar keratoplasty, Descemet's stripping endothelial keratoplasty [DSEK]).
7. Corneal refractive surgery (e.g., laser-assisted in situ keratomileusis [LASIK], photorefractive keratectomy [PRK], limbal relaxing incision [LRI]) within 12 months prior to Visit 1/Screening.
8. Cataract extraction, with or without minimally invasive glaucoma surgery (MIGS), within 90 days prior to Visit 1/Screening.
9. Cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal within 30 days prior to Visit 1/Screening or planned during the study. If a subject has a punctal plug at Visit 1/Screening for ≥ 30 days and it falls out during the study, it should be replaced with a new plug of the same type.
10. Contact lens wear.

Prior Medications

11. Use of isotretinoin (Accutane®) within 60 days prior to Visit 1/Screening.
12. Use of topical cyclosporine (Restasis®, Cequa®) or topical lifitegrast (Xiidra®) within 45 days prior to Visit 1/Screening.
13. Use of any of the following medications within 30 days prior to Visit 1/Screening:
    - Topical ophthalmic corticosteroids or topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs)
    - Autologous serum
    - Topical ophthalmic antibiotics or antivirals
    - Topical ophthalmic antihistamines or mast cell stabilizers
    - Topical ophthalmic medications for lowering of intraocular pressure (IOP) for treatment of glaucoma or ocular hypertension
    - Systemic immunosuppressive agents
    - Systemic (i.e., oral, intravenous, intra-articular, intrathecal, epidural, or intramuscular) corticosteroids (intranasal, inhaled, dermatologic, or peri-anal steroids are allowed)

- Tetracycline compounds (tetracycline, doxycycline or minocycline)

Current Medications

14. Any *changes* in the dosing of any chronically used systemic drug within 90 days prior to Visit 1/Screening and throughout the study period, including but not limited to the following:
    - Anticholinergics
    - Antidepressants including selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SSNRIs), tricyclics, and benzodiazepines
    - Antihistamines
    - Systemic H1-receptor antagonists
    - β-adrenoceptor antagonists
    - Calcium channel blockers
15. Any *changes* in the dosing of aspirin and aspirin-containing products within 30 days prior to Visit 1/Screening and throughout the study period.

General

16. Stevens-Johnson syndrome.
17. History of immunodeficiency disorder, HIV, positive hepatitis B, C, or evidence of acute active hepatitis A (anti–HAV IgM).
18. History of organ or bone marrow transplant.
19. History of graft versus host disease (GvHD).
20. Systemic lupus erythematosus.
21. Chronic pain syndrome (e.g., fibromyalgia).
22. Systemic signs of infection (e.g., fever or current treatment with antibiotics).
23. Serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes.
24. Known history of alcohol and/or drug abuse within 12 months prior to Visit 1/Screening that, in the opinion of the Investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject.
25. Known allergy or contraindication to any component of IP formulation or diagnostic agents.
26. Participation in any drug or device clinical investigation within 30 days prior to Visit 1/Screening and/or during the period of study participation.

27. Screening and enrollment of more than one individual who resides in the same household at the same time (participation is allowed after the other individual has been determined to be a screen failure or after the other individual has completed Visit 7/Day 84).
28. Screening and enrollment of employees of the clinical site.

5. STUDY TREATMENT(S)

5.1. Description of Treatment(s)

5.1.1. Study Drug

SDP-4 Ophthalmic Solution is a non-preserved aqueous solution of SDP-4 for topical ophthalmic use and will contain the active substance (SDP-4) and polysorbate-80, sodium acetate trihydrate, glacial acetic acid, magnesium chloride hexahydrate, and dextrose monohydrate.

5.1.2. Control

The vehicle solution will be the same as the SDP-4 except for the omission of the active substance (SDP-4).

All subjects who meet study entry criteria at Screening/Visit 1 (Day -14 ± 2) will receive a supply of vehicle solution prior to randomization to the double-masked study to be administered during the 14-day (± 2) screening/run-in period.

5.2. Selection, Timing and Administration of Dose for Each Patient

Subjects will be randomized to treatment with 1 of 3 concentrations (0.1%, 1.0% and 3.0%) of SDP-4 Ophthalmic Solution or vehicle which will be administered to each eye BID, approximately 12 hours apart, for 84 days.

Subjects (or their caregiver, if the subject is not able to self-administer the IP) will administer IP topically OU BID for 84 days. At the Screening and Baseline visits, site personnel will instruct the subject (or caregiver) in topical ocular drop administration procedures. After instilling a drop in each eye, the used single-use dose (SUD) should be stored in the storage container provided by site personnel and placed back in the box.

Twice each day, approximately 12 hours apart, the subject (or caregiver) will open a new SUD and administer 1 drop to each eye, store the used SUD in the foil pouch, and place it in the box (or storage container) for return to the clinical site so accountability can be documented in the source document and electronic case report form (eCRF). All IP, including the box, used SUDs/foil pouches and any unopened SUDs will be returned to the clinical site where the used and unopened IP will be documented at Visits 2 through 7.

5.3. Method of Assigning Patients to Treatment Groups

Subjects will be randomized in a 1:1:1:1 ratio to 0.1%, 1.0% or 3.0% SDP-4 or vehicle in parallel groups. A computer-generated randomization code for allocating the solutions will be prepared by an independent unmasked biostatistician not involved in the day-to-day running of the study.

If subjects meet eligibility criteria at Screening (Visit 1/Day -14) and Visit 2/Day 1 (see Section 4 for eligibility criteria), subjects will be randomly assigned to IP at Visit 2. Clinical sites will utilize the Interactive Web Response System (IWRS) to assign kits to subjects. The IP kit randomization number will be recorded in the subject's eCRF. The randomized IP may vary slightly in hue from nearly clear to a slight tint. This variability is normal.

5.4. Masking

The study will be double-masked. All SDP-4 concentrations and vehicle will be provided in SUDs seal packed into foil pouches which are enclosed in a box and dispensed in one-month supplies at Visits 2, 5, and 6. Subjects, the Investigator, and all site personnel responsible for performing study assessments will remain masked to treatment assignment.

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the Investigator may obtain the treatment code for a given randomized subject from the IWRS. The treatment code is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject.

The following procedure should be followed:

1. The Investigator should contact the Medical Monitor via phone immediately before unmasking a subject, unless it is not possible to do so without risk to the subject.
2. The Investigator should document the serious adverse event (SAE), if applicable, and justification for unmasking in the eCRF.
3. The subject may continue to participate in the study to be followed for safety at the Investigator's discretion. If the subject is to be discontinued from study participation, then ALL procedures described in the Early Discontinuation Visit (Section 7.3) should be completed.
4. The Investigator should contact Oculos Clinical Research (Oculos), the clinical research organization (CRO), at SilkTech-safety@oculoscr.com within 24 hours with the randomization number, subject initials, details of the adverse event (AE) or SAE, any action taken, and whether the subject is continuing in the study.

5.5. Concomitant Therapy

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the IP may be given at the discretion of the Investigator and in consultation with the Medical Monitor. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor.

If a subject complains of persistent dry eye symptoms, the site may provide the subject with unpreserved artificial tears (provided by the Sponsor), to be used only if necessary. The subject must return all used and unused artificial tears at each visit so the site can conduct accountability to assess the use of artificial tears. Artificial tears may not be used within 2 hours prior to any study visit; the subject may either be rescheduled or may wait at the site until 2 hours have passed since instillation if this occurs.

Permitted steroid medications include intranasal, inhaled, dermatologic, or peri-anal, steroids.

Whenever possible, medications should be administered in dosages that remain stable throughout the study duration. All concomitant medications will be recorded in the eCRF.

5.6. Restrictions

The Medical Monitor should be notified before prohibited medication or therapy is administered, unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration. The Medical Monitor should be contacted to determine the permissibility of a specific medication or therapy and whether or not the subject should continue with study participation.

5.6.1. Prohibited Medications and Treatments

The following medications are prohibited as specified:

Within 60 days prior to Visit 1/Screening and throughout the study duration:

- Use of isotretinoin (Accutane)

Within 45 days prior to Visit 1/Screening and throughout the study duration:

- Use of topical cyclosporine (Restasis, Cequa) or topical lifitegrast (Xiidra)

Within 30 days prior to Visit 1/Screening and throughout the study duration:

- Topical ophthalmic corticosteroids or topical ophthalmic NSAIDs
- Autologous serum
- Topical ophthalmic antibiotics or antivirals
- Topical ophthalmic antihistamines or mast cell stabilizers
- Topical ophthalmic medications for lowering of IOP for treatment of glaucoma or OHT
- Systemic immunosuppressive agents other than corticosteroids
- Systemic (oral, intravenous, intra-articular, intrathecal, epidural or intramuscular) corticosteroids
- Tetracycline compounds (e.g., tetracycline, doxycycline or minocycline)

Any *change* in the dosing of the following within 90 days prior to Visit 1/Screening and throughout the study duration:

- Anticholinergics
- Antidepressants including selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SSNRIs), tricyclics, and benzodiazepines
- Antihistamines
- Systemic H1-receptor antagonists
- β-adrenoceptor antagonists
- Calcium channel blockers

Any *change* in the dosing of the following within 30 days prior to Visit 1/Screening and throughout the study duration:

- Aspirin and aspirin-containing products

The following procedures are prohibited as specified:

Any previous:

- Reconstructive or cosmetic eyelid surgery that may affect the normal function of the lids (e.g., blepharoplasty, ptosis repair, entropion/ectropion repair)
- Invasive glaucoma (e.g., trabeculectomy, shunt) and/or corneal surgery (e.g., penetrating keratoplasty, lamellar keratoplasty, DSEK)

Within 12 months prior to Visit 1/Screening:

- Corneal refractive surgery (e.g., LASIK, PRK, LRI)

Within 90 days prior to Visit 1/Screening:

- Cataract extraction, with or without MIGS

Within 30 days prior to Visit 1/Screening and throughout the study period:

- Cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal. If a subject has a punctal plug at Visit 1/Screening for ≥ 30 days and it falls out during the study, it should be replaced with a new plug of the same type.

Contact lens wear prior to and during the study is prohibited.

5.6.2. Treatment Compliance

Treatment compliance will be monitored by IP accountability throughout the study. The amount of used and unused run-in vehicle returned at Visit 2/Day 1 and used and unused randomized IP returned at Visit 5/Day 28, Visit 6/Day 56, and Visit 7/Day 84 will be documented by site personnel. Additionally, the amount of used and unused artificial tears will be documented by site personnel starting at Visit 2 through Visit 7 if the artificial tears were required by the subject.

5.7. Packaging and Labeling

The IP will be filled into blow-fill-seal (BFS) containers composed of low density polyethylene (LDPE). The individual cartridges of 5 SUDs will be seal packed into a foil pouch. The foil-wrapped cartridges will be packaged 7 at a time into a cardstock storage box that will contain a total of 35 SUDs for the 2-week run-in period. The foil-wrapped cartridges will be packaged 16 at a time into a cardstock storage box that will contain a total of 80 SUDs dispensed monthly at Visits 2, 5 and 6 during the randomized treatment period. A label bearing the required IP labeling information per Code of Federal Regulations (CFR) Part 312, Section 312.6 will be added on the outside of the foil wrapping and the outside of the IP storage box.

5.8. Storage and Accountability

The IP should be stored at a controlled temperature at 15°- 25°C (59°-77°F) in a secured area. A temperature log will be maintained at each clinical site. Subjects should be instructed to store IP at home at room temperature. After opening a foil pouch, the remaining SUDs should be stored in the pouch until used. Subjects will retain all used and unused IP materials (SUDs, foil pouches, boxes) to return to the site.

5.9. Investigational Product Dispensing and Retention at Study Site

At Visit 1/Screening, if the eligibility criteria are met, vehicle solution for the screening/run-in period will be dispensed to the subject with instructions to return the used and unused IP at Visit 2/Day 1. When the run-in study materials are returned by the subject, accountability will be performed and the box will be retained at the site in a secured location.

At Visit 2/Day 1, Kit 1 will be dispensed after the subject is randomized. Kits 2 through 3 will remain in a secured location at the site. The subject will be instructed to return the box along with all used and unused IP study materials at Visit 5/Day 28.

At Visit 5/Day 28, when Kit 1 is returned by the subject, accountability will be performed and the kit will be retained at the site in a secured location. The site will dispense Kit 2 to the subject according to randomization number with instructions to return the box along with used and unused IP study materials at Visit 6/Day 56.

At Visit 6/Day 56, when Kit 2 is returned by the subject, accountability will be performed and the kit will be retained at the site in a secured location. The site will dispense Kit 3 to the subject with instructions to return the box along with used and unused IP study materials at Visit 7/Day 84.

At Visit 7/Day 84, when Kit 3 is returned by the subject, accountability will be performed and the kit will be retained at the site in a secured location for the clinical research associate (CRA) to perform IP accountability and reconciliation. At the end of the study, the site or CRA will ship the IP study materials back to the packager for destruction.

Note: If at any visit, the subject complains of persistent dry eye symptoms and a supply of artificial tears is provided, the subject must return all used and unused artificial tears at *each* subsequent visit so the site can perform accountability to assess the use of artificial tears/resupply artificial tears as needed.

6. STUDY PROCEDURES

6.1. Informed Consent

Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign, and date the current Institutional Review Board (IRB)-approved version of the informed consent form. A full discussion of informed consent is presented in Section 10.3.

6.2. Demographics and Background Characteristics

6.2.1. Demographics

Demographic information including age, gender, race, ethnicity, and date of informed consent will be recorded.

6.2.2. Medical/Ocular History

Clinically significant medical and ocular history will be documented and will include any previously diagnosed ocular abnormalities and ocular surgeries, including laser and non-laser procedures.

6.2.3. Medication History

All current medications (prescription and over-the-counter) taken at Screening, 90 days prior to Screening, and throughout the course of the study will be recorded in the Concomitant Medications page of the eCRF. Information regarding the dates of first and last dose, site of dosing (e.g., right eye, left eye, OU, systemic), and the reason the medication is being taken must be recorded in the eCRF.

6.2.4. Urine Pregnancy Test

A urine pregnancy test will be performed at Visit 1/Screening and Visit 2/Day 1 and repeated at Visit 7/Day 84 or the Early Discontinuation Visit for women of childbearing potential only.

6.3. Efficacy Assessments

Efficacy will be measured by assessment of DED symptoms (SANDE total score, individual symptoms rated on a visual analogue scale (VAS): itching, foreign body sensation, burning/stinging, fluctuating vision, eye dryness, eye discomfort, photophobia, and eye pain) and signs (TBUT, Schirmer's test [anesthetized], corneal fluorescein staining, conjunctival lissamine green staining, and conjunctival hyperemia). All efficacy assessments will be conducted at the timepoints shown on the Schedule of Visits and Examinations (Table 1).

6.3.1. Symptoms

6.3.1.1. SANDE (Symptom Assessment in Dry Eye) Questionnaire

The SANDE contains two questions regarding the frequency and severity of DED symptoms as shown in Figure 1.

Figure 1: Symptom Assessment in Dry Eye (SANDE) Questionnaire

1. Frequency of symptoms:

Please place a mark on the line to indicate how often, on average, your eyes feel dry and/or irritated:

Rarely All the time

2. Severity of symptoms:

Please place a mark on the line to indicate how severe, on average, you feel your symptoms of dryness and/or irritation are:

Very mild Very severe

Source: Schaumberg et al., 2007

The frequency and severity scores (SANDE) will be recorded in the eCRF. The total score is the square root of the frequency score times the square root of the severity score (range 0-100) and will be calculated by the electronic data capture (eDC) system.

6.3.1.2. Measurement of Individual Dry Eye Symptoms

The following individual symptoms of DED will be evaluated using a separate VAS scale for each symptom and will include: itching, foreign body sensation, burning/stinging, fluctuating vision, eye dryness, eye discomfort, photophobia, and eye pain.

The subject will be asked to make a mark on the line to indicate how he/she feels about each symptom since the last visit.

Itching

Doesn't itch at all Want to scratch my eyes out

Foreign Body Sensation

Don't feel like I have something in my eye Feel like I have sand in my eye

Burning/Stinging

Doesn't burn/sting at all Severe

Fluctuating Vision

Vision is fine Vision constantly changes

Eye Dryness

Not dry at all Extremely dry

Eye Discomfort

Very comfortable Extremely uncomfortable

Photophobia

Not sensitive to light Extremely sensitive to light

Eye Pain

No eye pain Need pain medicine

The score for each symptom will be recorded in the eCRF.

6.3.2. Signs

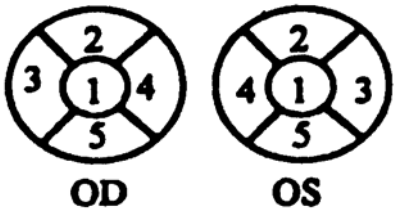
6.3.2.1. Tear Break-up Time

The tear film will be observed under the slit-lamp and timed until the tear film breaks up (i.e., tiny dry spots develop) (Nichols et al., 2004). The procedure is conducted 2 times for each eye and the TBUT for each is measured in seconds and recorded in the eCRF. The average for each eye will be calculated by the eDC system. Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.3.2.2. Corneal Fluorescein Staining

Following evaluation of TBUT, corneal fluorescein staining using a Wratten #12 filter (or equivalent) will be measured using the National Eye Institute (NEI) standardized grading system to grade each of the 5 areas of the cornea on a 0-3 scale (as shown in Figure 2)(range: 0 – 15) (Lemp, 1995). Consult the Study Reference Manual for specific details regarding the evaluation procedures.

Figure 2: Division of the Corneal Surface for Measuring Fluorescein Uptake



Source: Lemp, 1995

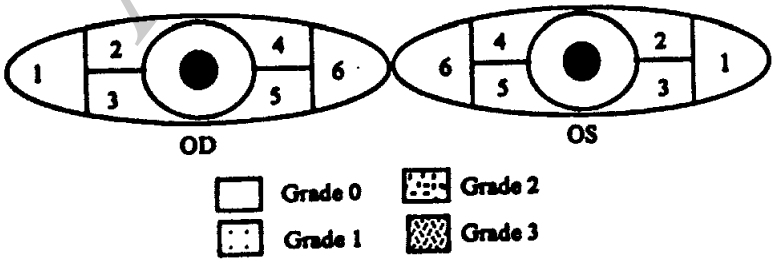
6.3.2.3. Conjunctival Hyperemia

Conjunctival hyperemia will be graded during the slit-lamp examination using the McMonnies photographic scale (McMonnies and Chapman, 1987a; McMonnies and Chapman, 1987b). This photographic reference scale consists of 6 levels or grades of conjunctival hyperemia (0 = none, 5 = severe). Please note that these were designed for contact lens wearers, but validated for non-contact lens wearers (McMonnies and Ho, 1991). Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.3.2.4. Conjunctival Lissamine Green Staining

After corneal staining, lissamine green conjunctival staining will be measured. Six (6) areas of the conjunctiva will be evaluated (Figure 3) (Lemp, 1995). The Investigator will record a score for each area of each eye. The scores for each eye will be summed, excluding superior zones 2 and 4. Consult the Study Reference Manual for specific details regarding the evaluation procedures.

Figure 3: Division of the Conjunctival Surface for Measuring Lissamine Green Staining



6.3.2.5. Anesthetized Schirmer's Test

An anesthetized Schirmer's test will be performed at least 5 minutes after the lissamine green conjunctival staining to allow for any reflex tearing to subside (Li et al., 2012; Tsubota et al., 1999). Following instillation of topical anesthetic, filter paper strips will be placed in both eyes inside the lower eyelid (conjunctival sac) at the same time. The eyes are closed for 5 minutes. The paper is then removed and the amount of moisture on each strip in

millimeters (mm) is measured and recorded in the eCRF (Wolffsohn et al., 2017). Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.4. Adverse and Serious Adverse Events

6.4.1. Definition of Adverse Events

6.4.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject administered an IP that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to this IP.

Note: IP in this study refers to all concentrations of SDP-4 and to the vehicle (control).

Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen after starting the investigational treatment. Abnormal test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the subject at each visit during the study. At each clinic visit, study personnel should ask the following question: "Have you had any problems since your last visit?" Adverse events also may be detected when they are volunteered by the subject during or between visits or through study assessments.

6.4.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening or sight-threatening

  Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity (excluding progression/outcome of the disease under study)
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is medically significant; i.e., defined as an event that jeopardizes the health of the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that is

unrelated to the indication under study and has not worsened since the start of the study, is not considered an SAE.

All SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until stabilization or resolution of the event.

6.5. Relationship to Investigational Product

The relationship of AEs to the IP should be assessed by the Investigator using the definitions below.

Not suspected: The temporal relationship of the event to the IP makes a causal relationship unlikely, or, other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the event to the IP makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, then the AE should be considered "suspected."

If the relationship between the AE/SAE and the IP is determined by the Sponsor to be "suspected" the event will be considered to be related to the IP for the purposes of expedited regulatory reporting.

6.6. Recording Adverse Events

Adverse events (AEs) spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, regardless of severity or potential association with the IP or study procedures, will be recorded in the eCRF. Changes from baseline assessments that are part of the disease being studied will not necessarily be recorded as AEs unless the Investigator deems them as such. Investigators are advised to consider reporting an increase in IOP of 10 mmHg or greater, or a visual acuity decrease of 3 lines EDTRS (15 letters) or greater as an AE. If ongoing at the time of the subject's last study visit, Investigators should follow the event until the subject has returned to baseline or the event has resolved.

All AEs that occur following consent and until the final study visit (Visit 7/Day 84) should be collected and recorded on the AE eCRF page. AEs that occur during the screening/run-in period (Visit 1/Day-14 ± 2 to Visit 2/Day 1) will be summarized separately from AEs that occur from the first dose of double-masked treatment on Day 1 to the Day 84 Visit or Early Discontinuation. Serious adverse events (SAEs) will be followed until the event is resolved or stabilized.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Onset (date)
- Resolution (date)
- Severity grade (mild, moderate, severe)
- Relationship to IP (not suspected, suspected)
- Action taken (none, IP temporarily interrupted, IP permanently discontinued; concomitant medication taken; hospitalization/prolonged hospitalization; other)
- Serious outcome (yes/no)

The severity grade should be determined by the Investigator using the definitions below:

- **Mild**: Discomfort noticed but no disruption of normal daily activity
- **Moderate**: Discomfort sufficient to cause interference with normal daily activity
- **Severe**: Incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as defined directly above) whereas seriousness is defined by the criteria under Section 6.4.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. The subject will stop using the IP, be withdrawn from the study, and followed through conclusion of pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

6.7. Reporting Adverse Events

All AEs (suspected and not suspected) will be recorded following consent and until the final study visit, Visit 7/Day 84. Any SAEs “suspected” to be related to the IP and discovered by the Investigator at any time after the study should be reported.

Any SAE that occurs must be reported within 24 hours of its occurrence or within 24 hours of learning of its occurrence by entering the information in the appropriate eCRF page in the EDC system. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed to SilkTech-Safety@oculoscr.com only if requested and after thorough de-identification/ removal of all personal health information (PHI). The Investigator must assess the SAE relationship to the IP/study treatment and severity and complete the SAE form. Silk Technologies/Oculos may request additional information. Follow-up information (e.g.,

discharge summary) will be retained in the subject's chart and a copy will be emailed to SilkTech-Safety@oculoscr.com.

In addition, all SAEs should be recorded on the Adverse Event eCRF page with the serious question marked "Yes".

All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

It is the Investigator's responsibility to notify the approving IRB of any site-specific SAEs per the IRB's reporting requirements.

Silk Technologies will report all SAEs to the United States (US) Food and Drug Administration (FDA) on the appropriate schedule depending if the event is IP related or not IP related, expected or unexpected (based on the available information in the IB).

Any death occurring during the study and follow up period should be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to IP, the SAE resulting in the death must be reported to Silk Technologies or designee. A death occurring after completion of the study does not require completion of the SAE form.

6.8. Other Safety Assessments

6.8.1. Best-Corrected Visual Acuity

Best-corrected visual acuity (BCVA) measurement will be performed in each eye at all study visits with the logMAR eye chart using the subject's best corrective lens prescription eyeglasses or trial frame lenses, if applicable. The subject's BCVA must be determined (via refraction) if corrected or uncorrected visual acuity is not logMAR 0.0 (equivalent to 20/20). This refraction must be used for all VA assessments for the duration of the study. The subject must wear the same glasses/trial frame, if applicable, at each visit. Ambient room lighting should be consistent for a given subject throughout the study period. Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.8.2. Biomicroscopy and External Eye Exam

A slit-lamp examination will be conducted at each study visit to assess the anterior ocular structures, including lid, cornea, conjunctiva, anterior chamber, iris, lens, and posterior capsule (if pseudophakic). Abnormalities will be documented. Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.8.3. Dilated Fundus Exam

A fundus exam consisting of the vitreous, optic nerve, macula, and peripheral retina will be conducted, and the structures will be graded as normal or abnormal. Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.8.4. Intraocular Pressure Measurement

Intraocular pressure will be measured utilizing a Goldmann tonometer. If possible, the same observer should perform the assessment and the same calibrated instrument should be used for a given subject throughout the study. To avoid IOP changes due to the diurnal rhythm, the

IOP measurements should be performed at approximately the same time of the day each time. Consult the Study Reference Manual for specific details regarding the evaluation procedures.

6.8.5. Investigational Product Comfort Assessment

Subjects will rate the comfort of IP instillation according to the following 4-point scale:

0 = No discomfort

1 = Mild discomfort

2 = Moderate discomfort

3 = Severe discomfort

6.9. Screen Failures

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria or met at least 1 of the exclusion criteria, and has not been randomized into the study. Based on Investigator discretion and Sponsor approval, subjects who initially failed to meet the inclusion/exclusion criteria may be rescreened at a later time if their eligibility status has changed. The subject will retain the same subject identification number that he/she was assigned at the first screening.

6.10. Subject Withdrawal Criteria

The following are the criteria for considering withdrawal from the study:

- Withdrawal of subject consent. The subject may request for any reason at any time to be withdrawn from the study.
- The Sponsor terminates the study.

If a subject withdraws from the study, the reason for withdrawal will be recorded in the eCRF.

If a study subject fails to attend a study visit at any point during the study period, every effort should be made to keep the subject in the study and conduct all study visits as scheduled; all attempts to contact the subject must be documented. If the subject relocates during the study period, the CRO should be contacted to determine if there is a possibility that the subject could continue at another clinical site.

6.11. Appropriateness of Measurements

The efficacy and safety assessments in this study are standard for ophthalmologic investigations, and their reliability, accuracy, and relevance is well established. Collection of AEs to monitor drug safety is standard in clinical studies.

7. STUDY ACTIVITIES

Table 1 provides a tabular summary of all scheduled visits and procedures to be performed during the clinical study.

7.1. Visit 1 (Day -14 ± 2/Screening Visit)

Procedures performed at Screening, Visit 1/Day -14 ± 2 will include the following:

- Obtain written informed consent
- Inclusion/exclusion criteria
- Demographics
- Medical and ocular history
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- SANDE
- BCVA (logMAR)
- Biomicroscopy/external eye exam
- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Anesthetized Schirmer's test
- IOP measurement
- Dilated fundus exam
- Re-review inclusion/exclusion criteria
- Dispense run-in medication/provide instruction on administration/in-clinic administration/evaluate administration
- AE assessment

Eligible subjects must have daily symptoms of DED for ≥ 6 months, a total score ≥ 40 on the SANDE questionnaire, history of artificial tear use in the 30 days prior to Screening, TBUT ≤ 6 seconds in both eyes, and anesthetized Schirmer's test tear volume ≥ 3 mm and <10 mm in both eyes.

If a subject complains of persistent dry eye symptoms after run-in medication is dispensed and between or during study subsequent visits, the site may provide the subject with unpreserved artificial tears (provided by the Sponsor), to be used only if necessary. The subject must return all used and unused artificial tears at each study visit so the site can conduct accountability to assess the use of artificial tears. Artificial tears may not be used

within 2 hours prior to any study visit; the subject may either be rescheduled or may wait at the site until 2 hours have passed since instillation if this occurs.

7.2. Treatment Period (Day 1 to Day 84 ± 4)

7.2.1. Visit 2 (Day 1/Confirmatory and Randomization Visit)

Procedures performed at Visit 2/Day 1 include:

- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- SANDE
- Individual symptom assessment (VAS)
- IP comfort assessment
- BCVA (logMAR)
- Biomicroscopy/external eye exam
- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Anesthetized Schirmer's test
- Review inclusion/exclusion criteria
- Randomize eligible subjects
- Dispense IP/provide instruction on administration
- Dispense artificial tears (if needed)
- AE assessment
- Run-in medication accountability
- Artificial tear accountability, if applicable

7.2.2. Visit 3 (Day 7 ± 2)

Procedures performed at Visit 3/Day 7 ± 2 include:

- Concomitant medication review
- SANDE
- Individual symptom assessment (VAS)
- IP comfort assessment
- BCVA (logMAR)
- Biomicroscopy/external eye exam

- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Dispense artificial tears (if needed)
- AE assessment
- Artificial tear accountability (if applicable)

7.2.3. Visit 4 (Day 14 ± 2)

Procedures performed at Visit 4/Day 14 ± 2 include:

- Concomitant medication review
- SANDE
- Individual symptom assessment (VAS)
- IP comfort assessment
- BCVA (logMAR)
- Biomicroscopy/external eye exam
- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Dispense artificial tears (if needed)
- AE assessment
- Artificial tear accountability (if applicable)

7.2.4. Visit 5 (Day 28 ± 2)

Procedures performed at Visit 5/Day 28 ± 2 include:

- Concomitant medication review
- SANDE
- Individual symptom assessment (VAS)
- IP comfort assessment
- BCVA (logMAR)
- Biomicroscopy/external eye exam
- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining

- IOP measurement
- Dispense IP
- Dispense artificial tears (if needed)
- AE assessment
- IP accountability
- Artificial tear accountability (if applicable)

7.2.5. Visit 6 (Day 56 ± 4)

Procedures performed at Visit 6 include:

- Concomitant medication review
- SANDE
- Individual symptom assessment (VAS)
- IP comfort assessment
- BCVA (logMAR)
- Biomicroscopy/external eye exam
- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Dispense IP
- Dispense artificial tears (if needed)
- AE assessment
- IP accountability
- Artificial tear accountability (if applicable)

7.3. Visit 7 (Day 84 ± 4) or Early Termination Procedures

At Visit 7/Day 84 ± 4 or the Early Termination Visit, all of the following end of treatment procedures must be completed:

- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- SANDE
- Individual symptom assessment (VAS)
- IP comfort assessment
- BCVA (logMAR)

- Biomicroscopy/external eye exam
- TBUT
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Anesthetized Schirmer's test
- IOP measurement
- Dilated fundus exam
- AE assessment
- IP accountability
- Artificial tear accountability (if applicable)

8. QUALITY CONTROL AND ASSURANCE

Silk Technologies and/or their contracted agents utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs require compliance with FDA regulations and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance.

The study will be monitored by CRAs/monitors to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, with ICH GCP, and with the applicable regulatory requirements.

To ensure compliance with GCP and all applicable regulatory requirements, Silk Technologies or its agent may conduct a quality assurance audit at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to: a review of all informed consent forms, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the study materials receipt, storage, and administration. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the findings of the audit.

9. STATISTICS

9.1. General Considerations

This is a Phase 2, multicenter, randomized, double-masked, vehicle-controlled, dose-response, parallel group study to evaluate the ocular and systemic safety and efficacy of SDP-4 ophthalmic solution in subjects with moderate to severe DED.

Subjects with DED are planned to be randomized to 1 of 3 concentrations of SDP-4 (0.1%, 1.0%, or 3.0%) or vehicle in a 1:1:1:1 ratio, with 75 subjects randomized to each group.

A biostatistician will perform statistical analyses as agreed with the Sponsor according to the Statistical Analysis Plan (SAP).

All continuous study assessments will be summarized by treatment and visit (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

All study data will be listed by treatment, subject, and visit (as applicable).

The unit of analysis for efficacy will be the study eye.

Efficacy analysis will be conducted on the intent-to-treat (ITT) population (primary efficacy analysis) and the per protocol (PP) population (secondary efficacy analysis). Safety analyses will be performed using the safety analysis population. Definitions for the analysis populations may be found in Section 9.3.

9.2. Determination of Sample Size

A sample size of 70 subjects per treatment group will have 80% power to detect a treatment difference of 11.7 units in SANDE total score and 1.2 seconds in TBUT at Visit 7/Day 84 using a t-test with a 0.05 two-sided significance level. This calculation is based on the assumptions shown in Table 2. Note: TBUT is one of several secondary outcomes planned to be analyzed, but the sample size was derived using assumptions based on expected SANDE and TBUT values. Over-enrollment of 5 subjects per group/20 subjects per study is planned to account for discontinuations.

Table 2 Sample Sizes: Two-Group t-test of Equal Means

Assumptions	SANDE	TBUT
Test significance level, α	0.050	0.050
1 or 2 sided test	2	2
Difference in means, μ_1-μ_2	11.684	1.192
Common standard deviation	24.500	2.500
Effect size, $\delta = \lvert\mu_1-\mu_2\rvert/\sigma$	0.477	0.477
Power (%)	80	80
n per group	70	70

9.3. Analysis Populations

9.3.1. Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects who received IP. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as randomized.

9.3.2. Per Protocol (PP) Population

The PP population is a subset of the ITT population, which will include all subjects who complete the study without major protocol deviations. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. The PP population will summarize subjects as treated.

9.3.3. Safety Population

The safety population will include all subjects who received IP. This population will be used to summarize safety variables and will summarize subjects as treated.

9.4. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized in tables. Summary tables will be supported with individual subject data listings.

9.5. Efficacy Endpoints and Analyses

9.5.1. Primary Efficacy Endpoint

Mean change from baseline in total SANDE score at Visit 7/Day 84

9.5.2. Secondary Efficacy Endpoints

- Mean and mean change from baseline at each visit for each of the following evaluations:
  - Conjunctival lissamine green staining (combined and each zone)
  - Corneal fluorescein staining (combined and each zone)
  - TBUT
  - Anesthetized Schirmer's test
  - Conjunctival hyperemia
  - Individual symptom VAS scores, separately for each symptom

- SANDE
  - Mean change from baseline in total SANDE score at each visit
  - Mean total SANDE score at each visit
  - Mean and mean change from baseline in each component of SANDE at each visit

9.5.3. Efficacy Analyses

The primary efficacy endpoint (SANDE) will be summarized using continuous summary statistics by treatment group and visit. The primary analysis will utilize a repeated measures mixed model where the dependent variable is the change from baseline score, treatment group is a fixed effect, baseline score is a covariate, and visit is a repeated measure on subject. The repeated measures mixed model is utilized to account for the effect of missing data under the assumption that the data are missing at random. Least squares means will be used to test each concentration of SDP-4 to vehicle. Sensitivity analyses for the primary endpoint will be performed using last observation carried forward (LOCF) as well as observed data only.

In order to minimize the impact of multiplicity in this dose-response study, the following hierarchy for analyses will be conducted (note: TBUT is one of several secondary outcomes planned to be analyzed, but the sample size was derived using assumptions based on expected SANDE and TBUT values):

1. Primary (SANDE) high concentration vs. vehicle
2. Primary (SANDE) middle concentration vs. vehicle
3. Primary (SANDE) low concentration vs. vehicle
4. Secondary (TBUT) high concentration vs. vehicle
5. Secondary (TBUT) middle concentration vs. vehicle
6. Secondary (TBUT) low concentration vs. vehicle

The comparisons will be conducted at $\alpha = 0.05$. Each comparison will be made in order until $P >$ (exceeds) 0.05. If $P \leq 0.05$, the comparison is statistically significant and testing is continued.

The planned analyses for all efficacy outcomes will be described in detail in the SAP, which will be finalized prior to database lock.

9.6. Safety Variables and Analysis

9.6.1. Safety Variables

Safety variables are as follows:

- Ocular and non-ocular AE monitoring
- BCVA

- Biomicroscopy
- Intraocular pressure
- Dilated fundus exam
- IP comfort assessment

9.6.2. Safety Analysis

Safety and IP comfort data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

AEs that occur during the screening/run-in period (Visit 1/Day-14 ± 2 to Visit 2/Day 1) will be summarized separately from AEs that occur from the first dose of double-masked treatment on Day 1 to the Day 84 Visit or Early Discontinuation.

The primary safety analysis will summarize ocular and non-ocular treatment-emergent adverse events (TEAEs) using discrete summaries at the subject level by system organ class and preferred term for each treatment group. A TEAE will be defined as occurring after the first dose of IP. Serious adverse events (SAEs) and treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

Biomicroscopy and dilated indirect ophthalmoscopy measures will be summarized by tabulating the distribution of score shifts between baseline and post-baseline assessments

Best-corrected visual acuity (BCVA; logMAR) and IOP (mm Hg) will be summarized at each visit, using continuous and discrete summary statistics, including change from baseline and the proportion of study eyes with pre-defined increases from baseline, specifically, eyes with a 3-line decrease in BCVA or eyes with ≥ 10 mm Hg increase in IOP.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Institutional Review Board (IRB) Approval

The IRB must review, approve, and provide continuing review of the clinical study protocol, protocol amendments, the informed consent documents, subject recruitment advertisements, and any other written information to be provided to the subjects. Initial IRB approval is an affirmative decision that the clinical study has been reviewed and may be conducted at the study site within the constraints set forth by the IRB, the institution, GCP, and applicable regulatory requirements. A copy of the IRB approval letter for the protocol, the informed consent, the intended advertising, and any written material to be provided to the subject must be submitted to Silk Technologies or designee prior to release of investigational supplies to the study site. Progress reports and notifications of serious adverse reactions will be provided to the IRB according to local regulations and guidelines. The IRB must be notified of completion or termination of the study. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

10.2. Ethical Conduct of the Study

The study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with ICH guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

10.3. Subject Information and Consent

A sample informed consent form containing the required elements of informed consent will be provided by Silk Technologies or designee. Any changes made to this sample must be approved by Silk Technologies or designee prior to submission to the IRB. After approval by Silk Technologies or designee, the informed consent form must be submitted to and approved by the IRB. The informed consent must be written in a language in which the subject is fluent. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation. The Investigator must forward a copy of the consent forms, the certified foreign language translation, and an IRB approval letter to Silk Technologies or designee.

It is the responsibility of the Investigator to inform each subject of the purpose of this clinical trial, including possible risks and benefits, and to document the informed consent process. Prior to undergoing any study-related procedures, the subject must read, sign, and date the current IRB-approved version of the informed consent form. The original informed consent form is to be retained by the study site, and a copy of the signed consent form is to be given to the subject.

10.4. Subject Confidentiality

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, Silk Technologies, Oculos, the IRB, and

FDA/relevant regulatory agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. No information that can be related to a specific individual subject will be released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

10.5. Study Monitoring

The study will be monitored by Silk Technologies or designee in accordance with current GCP to assure compliance with the study protocol and the quality of the data collected. Monitoring visits will occur as required and could include a study initiation visit, monitoring visit(s), and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct. The Investigator will be responsible for making sure that site personnel are provided adequate training on conducting delegated tasks.

Before a site can enter a subject into the study, a representative of the Sponsor will:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence and the responsibilities of the Sponsor and or its representatives

This study will utilize eDC to optimize the eCRF source verification process with limited separate source documentation. Monitors will review e-source data and overall study data/consistency remotely and query discrepancies based upon eCRF entries (eCRF initial entry is the source). During this monitoring, data are reviewed as entered by the site, and the monitors will flag any abnormalities, trends, or safety signals for Medical Monitor review and monitor follow-up onsite, if necessary. Refer to the Study Reference Manual and/or Regulatory Binder for details regarding the direct data entry of study assessments and requirements for maintaining additional source documentation via paper/medical record.

During visits to the study site, the monitor may review the source documents including but not limited to signed informed consent forms, inclusion/exclusion checklist, medical/ocular history, concomitant medications, study material accountability and storage, completed SANDE questionnaires and subject-completed VAS assessments, the reporting procedures for AEs, SAEs, and protocol deviations. The CRA will review the study documents maintained in the Regulatory Binder to ensure all documentation is current and only qualified and trained staff are appropriately delegated study related tasks. The CRA will also review the site-specific processes and research-related SOPs to ensure appropriate Investigator oversight is being maintained and documented as required by GCP/ICH.

All data generated during this study and the medical records/documents from which they originated are subject to inspection by the Sponsor or designee, the FDA, and other regulatory agencies. The Investigator must notify the Sponsor or designee promptly of any inspections scheduled by regulatory authorities.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the IP and other supplies have been accounted for (returned/destroyed), and ensure that the Investigators are aware of their responsibilities once the study ends.

The Investigator is responsible for permitting the Sponsor or designee direct access to any study documents for monitoring and auditing purposes, for providing adequate space for monitoring, and for addressing any questions or issues that might be raised by the monitor or auditor on a timely basis.

10.6. Case Report Forms and Study Records

Data relating to study procedures may be entered by site personnel directly onto eCRFs available in the study's eDC system. When the eCRF is the first study data is recorded, it will be the source document; exceptions are detailed in the Study Reference Manual. Paper source documents will be retained at the study site when appropriate.

10.7. Protocol Deviations

The Investigator should not deviate from the requirements of this protocol except in the event of a medical emergency.

A reportable protocol deviation is defined as nonadherence to the protocol that involves inclusion/exclusion criteria, affects subject safety, or has the potential to affect the integrity of the data. All protocol deviations will be reported to Silk Technologies by entering the event in the appropriate eCRF page. Protocol deviations should be reported to the IRB in accordance with IRB-specific guidelines. If there is any question as to whether the deviation is reportable, Silk Technologies or designee and the IRB should be contacted.

All changes to the protocol will be made by the Sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

10.8. Access to Source Documentation

A trial-related monitoring audit, review by the IRB, and/or regulatory inspection may be conducted at any time during or after completion of a study (Section 8). The Investigator will be given adequate notice if he/she is selected for an audit and must provide direct access to study documentation. The audit may include, but is not limited to, a review of all informed consent forms; a review of medical records; a review of regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the study materials receipt, storage, and administration.

10.9. Data Generation and Analysis

Management of data and the production of the clinical study report will be the responsibility of Silk Technologies or its designee.

During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Such clarifications

and corrections will be discussed with and approved by site personnel and appropriately documented. Prior to database lock, data listings will be generated, and anomalous values investigated.

10.9.1. Retention of Data

Investigators should retain study-related records at the site until informed by the Sponsor. The Investigator will not move study documents or discard any records without notifying Silk Technologies. If the Principal Investigator moves from the current clinical site, Silk Technologies should be notified of the name of the person who will assume responsibility for maintenance of the records at the clinical site or the new address at which the records will be stored. The Investigator will notify Silk Technologies as soon as possible in the event of accidental loss or destruction of any study documentation. If it becomes necessary for Silk Technologies or designee, or the FDA or relevant regulatory authorities to review any documentation relating to the study, the Investigator must permit access to such records.

10.10. Publication and Disclosure Policy

All information concerning SDP-4 and the operations of Silk Technologies, such as patent applications, formulas, manufacturing processes, basic scientific data or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of Silk Technologies. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of Silk Technologies

The publication policy is addressed in a separate agreement.

11. REFERENCE LIST

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12. SUMMARY OF CHANGES

12.1. Changes Implemented in Protocol SDP-4-CS201 Amendment 1

The following substantive changes were made to the original protocol:

Location	Description of Change	Rationale for Change
Synopsis Inclusion Criteria; 4.2. Inclusion Criteria; 7.1. Visit 1 (Day -14 ± 2/Screening Visit)	Change Anesthetized Schirmer's test tear volume ≥ 4 mm and <10 mm in both eyes." to Anesthetized Schirmer's test tear volume ≥ **3** mm and <10 mm in both eyes."	To allow for greater flexibility in enrollment of subjects.
Synopsis Exclusion Criteria; 4.3. Exclusion Criteria; 5.6.1. Prohibited Medications and Treatments	Add If a subject has a punctal plug at Visit 1/Screening for ≥ 30 days and it falls out during the study, it should be replaced with a new plug of the same type.	To clarify that punctal plugs that fall out from the eye during the study must be reinserted.
Synopsis Exclusion Criteria; 4.3. Exclusion Criteria; 5.6.1. Prohibited Medications and Treatments	Change The following medications are prohibited within 30 days prior to Visit 1/Screening and throughout the study duration: • Systemic (i.e., oral, intravenous, intra-articular, or intramuscular) corticosteroids (intranasal, inhaled, dermatologic, peri-anal, ~~or intrathecal~~ steroids are allowed) to • Systemic (i.e., oral, intravenous, intra-articular, **intrathecal, epidural,** or intramuscular) corticosteroids (intranasal, inhaled, dermatologic, **or** peri-anal steroids are allowed)	To clarify that intrathecal and epidural steroids are considered systemic steroids, and therefore prohibited within 30 days of Screening and throughout the study period.

Note that administrative and editorial changes were made to the protocol for consistency and clarity. Such changes are not itemized.

APPENDIX A. SPONSOR SIGNATURES

Study Title:	A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group, Dose-Response Study of SDP-4 Ophthalmic Solution in Subjects with Dry Eye Disease (DED)
Study Number:	SDP-4-CS201
Final Date:	03 April 2019

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed:_____ Date: 03 April 2019

Brian Lawrence, PhD
Chief Executive Officer
Silk Technologies, Ltd.

Signed:_____ Date: 03 April 2019

Charles Slonim, MD
Medical Monitor
Oculos Clinical Research

APPENDIX B. INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group, Dose-Response Study of SDP-4 Ophthalmic Solution in Subjects with Dry Eye Disease (DED)
Study Number:	SDP-4-CS201
Final Date:	03 April 2019

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date