Clinical Trial Protocol: ST-603-010

Study Title:	A Multicenter, Randomized, Double-Masked, Vehicle-Controlled Pilot Study of the Efficacy and Safety of Cyclosporine A Ophthalmic Solution (ST-603), 0.1% and 0.2% Compared to Vehicle in Subjects With Dry Eye Disease
Study Number:	ST-603-010
Study Phase:	Pilot
Product Name:	Cyclosporine A Ophthalmic Solution 0.1% (ST-603) and Cyclosporine A Ophthalmic Solution 0.2% (ST-603)
Indication:	Dry eye disease
Investigators:	Multicenter
Sponsor:	
Medical Monitor:	
Original Protocol:	

SYNOPSIS

Sponsor: Sirion Therapeutics, Inc.
Name of Finished Product: Cyclosporine A Ophthalmic Solution, 0.1% and Cyclosporine A Ophthalmic Solution, 0.2%
Name of Active Ingredient: Cyclosporine A
Study Title: A Multicenter, Randomized, Double-Masked, Vehicle-Controlled Pilot Study of the Efficacy and Safety of Cyclosporine A Ophthalmic Solution, 0.1% and 0.2% (ST-603) Compared to Vehicle in Subjects With Dry Eye Disease
Study Number: ST-603-010
Study Phase: Pilot
Primary Objective(s): To assess the efficacy and safety of cyclosporine A 0.1% and cyclosporine A 0.2% compared to vehicle for the treatment of dry eye disease
Study Design: This will be a multicenter, randomized, double-masked, vehicle-controlled, pilot trial. Subjects will be randomized to one of the following treatment arms and treated for 90 days: • CSA 0.1%: 1 drop administered per eye twice daily (BID) (n=65) • CSA 0.2%: 1 drop administered per eye BID (n=65) • Vehicle: 1 drop administered per eye BID (n=65) Subjects will be evaluated for safety and efficacy during the treatment period at Days 14 (± 3 days), 28 (± 3 days), 42 (± 3 days), 60 (± 3 days), and 90 (± 3 days). Both eyes will be assessed at all study visits. The study eye will be the eye with the higher summed corneal fluorescein staining score (type+extent/surface area+depth) at baseline; if both eyes score equally, the right eye will be chosen.
Study Population: Approximately 195 evaluable subjects will be enrolled at approximately 20 clinical sites in the United States. **Inclusion Criteria:** 1. Subjects ≥2 years of age 2. Documented medical history of dry eye disease for a period of at least 6 months 3. Use of artificial tears for at least 3 months prior to screening 4. Best-corrected visual acuity (BCVA) better than 20/400 in both eyes 5. Provision of signed, written consent prior to participation in any study-related procedures; or signed written consent from parent or legal guardian if the subject is a

minor and signed written assent from minor subject, if appropriate

Exclusion Criteria:

1. Previous use of CSA 0.05% (Restasis®) within the 3 months prior to screening
2. Previous treatment failure on CSA 0.05% (Restasis®)
3. Current use of systemic cyclosporine
4. Systemic and topical ophthalmic medications that are known to cause dry eye disease are prohibited and must not have been taken within 7 days of screening. These include the following medications:
   - Immunomodulators (permitted if dose is stable for 3 months prior to screening and not expected to change during the study period)
   - General anesthetics
   - Antihistamines (including over-the counter [OTC])
   - Cholinergics
   - Antimuscarinics
   - Tricyclic antidepressants
   - Phenothiazines
5. Any topical ophthalmic medications other than the assigned study medication or the provided artificial tears (Refresh Plus®)
6. Current active eye disease, other than dry eye disease (ie, any disease for which topical ophthalmic medication is necessary)
7. Abnormal lid position or closure in both eyes
8. End-stage lacrimal disease (Schirmer test score with nasal stimulation of <3 mm/5 min) or dry eye disease as the result of destruction of conjunctival goblet cells or scarring
9. Presence or anticipated use of punctal occlusion in the study eye
10. Intraocular or refractive surgery (including cataract extraction, LASIK, vitrectomy, or trabeculectomy) in the study eye within 3 months prior to study start
11. Unwilling to discontinue use of contact lenses during the duration of the study
12. Pregnancy or lactation, confirmed by urine pregnancy test. The test will be conducted if the Investigator deems it necessary.
13. Presence or history of any systemic or ocular disorder or condition that could possibly interfere with the interpretation of the study results in the study eye
14. HIV positive or diagnosis of AIDS
15. Known hypersensitivity to any component of the study or procedural medications
16. Participation in any other clinical trial within 30 days prior to screening
17. Unable to reliably report symptoms and history

Study Drug, Dose, and Mode of Administration:
CSA ophthalmic solution, 0.1% or 0.2%, or vehicle instilled as 1 drop per eye BID for 90 days

Duration of Treatment:
90 days

Efficacy Assessments:

Primary Efficacy Endpoints
The primary efficacy endpoints will be assessed as a comparison between groups in change

from baseline in the following:

- Lissamine green staining scores on Day 90
- Frequency of stickiness scores as rated on a 0–3 scale (0=never, 1=sometimes, 2=often, 3=constantly) on Day 90

Secondary Efficacy Endpoints
Secondary efficacy endpoints will be assessed as a comparison between groups in change from baseline and proportion of subjects for the following the endpoints:

- Central corneal clearing defined as a score of 0 in stain intensity in area 1 (area 1=central cornea, defined as central 5 mm of the cornea) at all time points in corneal fluorescein staining
- Total score of 0 in stain intensity in areas 1, 2, 3, and 4 (1 [central]+2 [temporal]+3 [inferior]+4 [nasal]=0) at all time points in corneal fluorescein staining
- Summed score of 0 (type+extent/surface area+depth=0) at all time points in corneal fluorescein staining
- Summed score of 0 (cornea+nasal conjunctiva+temporal conjuctiva=0) at all time points in corneal and conjunctival lissamine green staining
- Change of ≥10 mm in Schirmer test (anesthetized) score at all time points
- Individual and summed symptom frequency scores for burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation at all time points, rated on a 0-3 scale where 0=never, 1=sometimes, 2=often, and 3=constantly; maximum score=21
- Individual and summed symptom intensity scores for burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation as measured by the Visual Analogue Scale (VAS), rated on a 0-100 scale where 0=absent and 100=severe

Safety Assessments:
Safety assessments will include best-corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP), ophthalmoscopy, and recording of adverse events (AEs). An evaluation of subject comfort and tolerability following the instillation of the first and last dose of medication also will be performed.

Statistical Methods:

For all primary endpoints, comparison between groups will be made for change from baseline, mean, and standard deviation. Analysis will utilize data from the study eye only to assess the significance of the difference between CSA 0.1% or 0.2% compared to vehicle.

For all secondary endpoints, comparison between groups will be made for change from baseline, mean and standard deviation, and proportion of subjects meeting the endpoints. Analysis will utilize data from the study eye only to assess of the difference between CSA 0.1% or 0.2% compared to vehicle.

A two-sided alpha level of 0.05 will be used for the statistical testing of these endpoints.

The planned sample size is approximately 195 evaluable subjects.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
BCVA	best-corrected visual acuity
BID	2 times a day
BSS	balanced salt solution
CI	confidence interval
CRF	case report form
CSA	cyclosporine A
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IOP	intraocular pressure
ITT	intent-to-treat
LASIK	laser-assisted in situ keratomileusis
LC-MS/MS	liquid chromatography– tandem mass spectrometry
LDPE	low density polyethylene
LOCF	last observation carried forward
MLR	mixed lymphocyte reaction
OTC	over-the-counter
PP	per protocol
QID	4 times a day
RA	rheumatoid arthritis
SAE	serious adverse event
SOP	standard operating procedures
VAS	Visual Analogue Scale
VKC	vernal keratoconjunctivitis

1 INTRODUCTION

1.1 Background and Rationale for the Use of Cyclosporine A 0.1% and Cyclosporine A 0.2% for the Treatment of Dry Eye Disease

Dry eye disease is a disorder of the tear film due to tear deficiency or excessive tear evaporation that causes damage to the interpalpebral ocular surface. Most forms of dry eye disease include the following symptoms of ocular discomfort:

- Soreness, scratchiness, dryness, grittiness, and burning;
- Interpalpebral surface damage;
- Tear film instability; and
- Tear hyperosmolarity.

Any modifications of the lipid, aqueous, or mucus components of the tear film may affect the homeostasis of the ocular surface, leading to dry eye disease. In patients with dry eye, increased numbers of certain cytokines and matrix metalloproteases are found in the tears and elevated levels of T-lymphocytes are present in ocular surface tissues (Barber, 2005; Pflugfelder, 1999; Smith V.A., 2001; Solomon, 2001; Stern, 2002). These factors, combined with tear film instability, can lead to ocular surface damage and to suppression of lacrimal gland function.

Cyclosporine A (CSA) has been proposed as one of the most promising molecules with immunomodulatory and anti-inflammatory properties for the treatment of dry eye disease. CSA acts by binding an intracellular protein that ultimately controls transcription factors required for cytokine production and T-lymphocyte maturation, and also inhibits mitochondria-mediated apoptosis (Barber, 2005; Halloran PF, 1998; Klee CB, 1998). By suppressing the immune-based inflammation of the ocular surface, treatment with CSA allows the lacrimal glands to produce tears, potentiating the return of a more stable tear film and normal ocular surface.

Topical ophthalmic emulsions containing 0.05%, 0.1%, 0.2%, and 0.4% concentrations of CSA have previously been evaluated in various preclinical and clinical studies and have been shown to be safe and well tolerated. Additionally, information regarding studies for Restasis® (cyclosporine ophthalmic emulsion, 0.05%) was submitted to the Agency in support of NDA 21-023. Restasis studies showed significant improvement in subjects' tear production and fluorescein staining scores when compared with vehicle.

1.2 Description of the Investigational Products: Cyclosporine A 0.1% and Cyclosporine A 0.2%

The study drug being evaluated, ST-603, is a topical ophthalmic solution containing CSA at a concentration of 0.1% or 0.2% in a proprietary vehicle solution containing a preservative and surfactants. In order to increase ocular comfort and maximize stability, the formulation has been modified from the original ophthalmic CSA drug product developed by Laboratorios Sophia S.A. of Guadalajara, Mexico (Sophia Laboratories), which received marketing

approval in 2003 from the Mexico Ministry of Health (Modusik-A Ofteno®) for the treatment of dry eye conditions.

1.3 Nonclinical Studies With Cyclosporine A 0.1% and Cyclosporine A 0.2%

Two randomized toxicology studies in New Zealand white rabbits were conducted by Sophia Laboratories to evaluate the topical and ocular toxicity of the CSA ophthalmic formulation. The first study compared the topical toxicity of CSA 0.1% and CSA 0.05% to vehicle when dosed twice daily (BID) for 4 weeks in New Zealand white rabbits. The second study was conducted to evaluate long-term toxicity of CSA 0.1% dosed BID for 6 months in New Zealand white rabbits. Macroscopic examination and histopathologic tissues showed no appreciable differences in the eyes of the CSA-treated animals when compared to the eyes of the controls.

Another study examined the ocular and systemic toxicity of cyclosporine emulsions at 0.1%, 0.2%, and 0.4% concentrations in beagle dogs for 52 weeks (Restasis NDA 21-023). Control animals received the vehicle for CSA 0.4%. Eye drops were instilled in the left eye, and the right eye served as the untreated control. The treatment showed lacrimation to the treated eye due to placebo and the CSA emulsions, with CSA 0.4% showing the most lacrimation. Redness to conjunctiva was also observed in the treated eye at CSA concentrations of 0.1 to 0.4%. Although placebo- treated animals showed redness, the prevalence was low. No other treatment-related toxicity was observed in the eye or in other organs examined. Published data suggest that the IC_{50} for mixed lymphocyte reaction (MLR) for CSA is 40 ng/mL in dogs in vitro. These data suggest that ophthalmic doses of CSA would not show systemic immunosuppression.

In an additional chronic ocular toxicity study, cyclosporine ophthalmic emulsions at 0.05%, 0.2% and 0.4% concentrations were instilled into the left eye for 6 months in male and female rabbits (Restasis NDA 21-023). Control animals received vehicle only. The right eye served as the untreated control. With CSA 0.4% administered 6 times daily, iritis (slight-mild) and miosis were observed in the treated eye during the first week of treatment. Conjunctival discomfort (slight to mild) and conjunctival hyperemia (slight) were also observed in the placebo-treated and CSA-treated rabbits. Slight conjunctival discharge was also observed in CSA-treated animals. Inflammation with mononuclear cell infiltration was observed in both eyes in the drug-treated and placebo-treated animals in the upper and lower eyelids, and lacrimal and Harder's glands. No histological abnormality due to the CSA emulsion was noted in the iris, ciliary body, lens, retina, sclera, choroid, optic nerve, extraocular muscle, and other nonocular tissues. The systemic level of CSA when CSA 0.4% emulsion was dosed at 1 drop 6 times per day in whole blood was [redacted]- ng/mL. The systemic trough level in whole blood in rheumatoid arthritic subjects is 97 ng/mL. Data suggest that CSA systemic exposure was minimal in dogs and rabbits compared to oral doses in RA subjects following ophthalmic delivery of CSA emulsions. There is no evidence of CSA-related toxicity to eyes and other organs following the chronic treatment with the CSA ophthalmic formulation.

1.4 Clinical Studies With Cyclosporine A 0.1% and Cyclosporine A 0.2%

1.4.1 Sophia Laboratories

Sophia Laboratories conducted 4 controlled clinical trials (SL-1, SL-2, SL-3, and SL-4) of CSA topical ophthalmic solution at 0.1% and 0.05% concentrations.

The initial study, SL-1, evaluated CSA 0.1% (Modusik-A Ofteno) in 45 healthy volunteers dosed twice daily for 14 days. Adverse events (AEs) were minimal with 1 to 2 subjects demonstrating slight conjunctival hyperemia at various study visits, but all subjects were free of hyperemia by Day 15. No clinically significant variations in IOP were seen. The conclusion was that CSA 0.1% (Modusik-A Ofteno) could be safely administered BID for 14 days.

Study SL-2 was a double-masked Phase 2/3 trial assessing the safety, efficacy, and tolerability of CSA 0.1% versus 0.05% versus vehicle in 117 subjects with moderate to severe dry eye. Study medication was dosed twice daily for 120 days. Of the CSA-treated subjects (0.05% and 0.1% combined), 100% showed improvement in the corneal surface, and clinically significant improvement was seen in several dry eye symptoms in the combined CSA treatment groups (ie, CSA 0.1% and 0.05%) in comparison to vehicle.

Study SL-3 was a Phase 3 crossover study performed in 100 subjects (196 eyes) diagnosed with moderate to severe dry eye disease, with or without Sjögren syndrome. This was a multicenter, longitudinal, comparative, randomized, double-masked study evaluating CSA 0.1% compared to placebo (vehicle). The results demonstrated that CSA 0.1% was well tolerated. Statistically significant improvement in Schirmer test scores was shown in the CSA group compared to vehicle on Day 21 ($P = 0.024$) but the differences did not reach significance for the remaining study visits except for the Day 42 visit which showed a strong trend with $P = 0.053$. Other efficacy endpoints (hyperemia, Rose Bengal staining, dry and burning sensation, fluorescein staining) showed improvements over the study period between the 2 study groups.

The fourth study, SL-4, examined the efficacy and tolerability of CSA 0.1% and 0.05% compared to olopatadine HCl ophthalmic solution 0.1% in children and young adults with allergic conjunctivitis (Gonzalez, unpublished manuscript). The trial included 199 subjects who were treated BID with the allocated treatment for 6 months. While most parameters did not show statistically significant differences between the 3 treatment groups, treatment with CSA 0.1% produced greater reductions in ocular discharge, hyperemia, papillae, follicles, chemosis, quantity of secretions, and corneal staining. The difference between CSA 0.1% and 0.05% was statistically significant for chemosis at Day 60 ($P = 0.024$). The only adverse events reported were 2 cases of slight superficial punctuate keratitis (1 possibly related to CSA, the other to olopatadine), and 1 case of acute bacterial conjunctivitis, possibly due to CSA.

1.4.2 Stevenson, 2000

In a dose-ranging study of the safety, efficacy, and tolerability of CSA ophthalmic emulsion, CSA concentrations of 0.05%, 0.1%, 0.2%, or 0.4% were administered to subjects with moderate-to-severe dry eye disease (Stevenson, 2000). In this study, 162 randomized subjects self-instilled study medication (CSA 0.05%, 0.1%, 0.2%, 0.4%, or vehicle) into both eyes twice daily for a period of 12 weeks, then were followed with post-treatment observation for 4 weeks. In all treatment groups, no significant adverse effects were reported. Additionally, all CSA concentrations yielded minimal systemic absorption as detected by a highly sensitive, liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay designed to reveal cyclosporine levels in the blood as low as 0.1 ng/mL. Although no particular efficacy-related benefits were shown among subjects utilizing CSA concentrations higher than 0.1%, all concentrations were found to be safe and well tolerated.

1.4.3 Studies ST-603-005 and ST-603-007

Sirion Therapeutics conducted 2 similar Phase 3 studies comparing a topical CSA 0.1% formulation to vehicle in the treatment of subjects with moderate-to-severe dry eye disease (Data on File, 2008). A total of 522 subjects were randomized to receive either ST-603 or vehicle dosed in the study eye (the eye designated by the worst Schirmer test score) at 1 drop BID for 42 days. In the group receiving CSA 0.1%, improvements were observed in a number of objective and subjective measures, including mean lissamine green staining score for the cornea and conjunctiva, mean total corneal fluorescein staining, mean symptom frequency scores for burning/stinging and stickiness, and mean intensity score for stickiness. Overall, CSA 0.1% administered BID was considered by the Investigators to be safe and well tolerated in subjects with moderate-to-severe dry eye disease.

1.4.4 Pucci, 2002

Another 4-month trial evaluated the safety and efficacy of CSA 2% eye drops in the treatment of vernal keratoconjunctivitis (VKC) in child-subjects (Pucci, 2002). The study population was composed of 24 children who had experienced signs and symptoms of severe VKC for at least one year prior to the study. Subjects were randomized to receive 1 drop of CSA 2% in 1 eye and 1 drop of vehicle in the fellow eye, administered 4 times a day (QID), over a 2-week period; the initial 2-week period of the study comprised the double-masked, placebo-controlled portion of trial. For the remaining 3 months and 2 weeks, the trial continued in open fashion with 1 drop of CSA 2% being dosed QID in both eyes. Although several subjects reported symptoms of mild-to-moderate burning and tearing for 15 to 40 minutes after administration, these symptoms tended to diminish or disappear within the first 2 to 3 weeks. These same symptoms also were reported in the placebo-treated eye by subjects. At no time did any subject discontinue use of the study medication. Based on statistical analysis of both the objective and subjective scores in this 4-month study, CSA 2% was found to be safe and efficacious for the treatment of children with severe VKC.

1.5 Justification for Dose, Regimen, and Treatment Period

The selection of CSA 0.1% and CSA 0.2% in this current protocol is based on: 1) the CSA 0.1% concentration and twice daily dosing regimen evaluated in Sirion Therapeutic's studies ST-603-005 and ST-603-007 (Data on File, 2008), and 2) the potential for CSA to demonstrate increased efficacy when dosed twice daily at a 0.2% concentration. The 90-day treatment period allows adequate assessment of efficacy of the investigational drug concentrations being compared. This study is also designed to compare points of safety regarding the 0.1% and 0.2% concentrations.

Additionally, Sirion Therapeutic's new formulation of ST-603 is being investigated in this study for its potential to increase ocular comfort, and, thereby, enhance overall patient tolerability and compliance.

1.6 Good Clinical Practices Statement

This study will be conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and all applicable local and US federal regulatory requirements.

1.7 Population to Be Studied

Study subjects will have a documented history of dry eye disease for at least 6 months, will be ≥2 years of age, and will reside in the US. Informed consent will be obtained prior to enrollment in the trial.

2 STUDY OBJECTIVE

2.1 Primary Objective

The primary objective of this study is to compare the safety and efficacy of CSA 0.1% and CSA 0.2% to vehicle in subjects with dry eye disease.

3 INVESTIGATIONAL PLAN

3.1 Trial Design and Description

This will be a multicenter, randomized, double-masked, vehicle-controlled, pilot trial to assess the safety and efficacy of CSA 0.1% and CSA 0.2% to vehicle for the treatment of dry eye disease. The study duration is 90 days. Subjects will be allocated to the CSA 0.1%, CSA 0.2%, or vehicle treatment groups and will instill the study drug at a dose of 1 drop per eye BID. The treatment bottles and treatment schedule will be arranged so that all subjects will follow the same procedures and have the same number of instillations per day, to maintain subject masking.

Screening/baseline evaluations will be conducted on Day 0, at which time subjects must meet inclusion requirements. At this visit, study site personnel will obtain informed consent, demographic information, medical history, and ocular history; assess the subject for inclusion and exclusion criteria; and perform the following measures: corneal fluorescein staining, lissamine green staining, Schirmer test (anesthetized), symptom frequency rating, symptom intensity rating (VAS), best-corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP), ophthalmoscopy, and prior and concomitant medications assessment.

Subjects who meet eligibility criteria will be randomized to CSA 0.1%, CSA 0.2%, or vehicle and will begin the treatment phase. Both eyes will be treated and evaluated. After the first instillation of the study medication and at Day 90, an evaluation of the subject's comfort and tolerability will be performed.

Artificial tears (Refresh Plus®) will be dispensed to subjects for use during the treatment period. **Subjects will be instructed to use the artificial tears only as needed up to 8 times per day. Subjects also will be instructed not to use the artificial tears within 30 minutes of instilling the study drug.**

Safety and efficacy assessments will be conducted on Days 14 (±3 days), 28 (±3 days), 42 (±3 days), 60 (±3 days), and 90 (±3 days). Subjects will be evaluated for primary efficacy on Day 90. See Appendix 1, Schedule of Events, for a listing of all study-related procedures to be conducted at each visit.

3.2 Trial Endpoint

Both eyes will be assessed at all study visits. The study eye, the eye with the higher, summed fluorescein corneal staining score (type+extent/surface area+depth) at baseline, will be selected for all efficacy analyses. If both eyes score equally, the right eye will be chosen by default as the study eye.

3.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints will include comparison between groups in change from baseline at Day 90 in the following:

- Lissamine green staining scores

- Frequency of stickiness scores as rated on a 0–3 scale (0=never, 1=sometimes, 2=often, 3=constantly)

3.2.2 Secondary Efficacy Endpoints

Exploratory secondary efficacy endpoints will include between-group comparison in change from baseline and proportion of subjects for the following:

- Central corneal clearing defined as a score of 0 in stain intensity in area 1 (area 1=central cornea, defined as central 5 mm of the cornea) at all time points in corneal fluorescein staining
- Total score of 0 in stain intensity in areas 1, 2, 3, and 4 (1 [central]+2 [temporal]+3 [inferior]+4 [nasal]=0) at all time points in corneal fluorescein staining
- Summed score of 0 (type+extent/surface area+depth=0) at all time points in corneal fluorescein staining
- Summed score of 0 (cornea+nasal conjunctiva+temporal conjuctiva = 0) at all time points in corneal and conjunctival lissamine green staining
- Change of ≥10 mm in Schirmer test (anesthetized) score at all time points
- Individual and summed symptom frequency score for burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation at all time points, rated on a 0-3 scale where 0=never, 1=sometimes, 2=often, and 3=constantly; maximum score=21
- Individual and summed symptom intensity score for burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation as measured by the Visual Analogue Scale (VAS), rated on a 0-100 scale where 0=absent and 100=severe

3.2.3 Safety Variables

Safety variables include best-corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP), ophthalmoscopy, and recording of adverse events (AEs). An evaluation of subject comfort and tolerability following the instillation of the first and last dose of medication also will be performed.

3.2.3.1 Subject Comfort and Tolerability

An evaluation of subject comfort and tolerability following the first (Day 0) and last (Day 90) instillations of the study medication will be performed.

3.3 Study Duration and Dates

The duration of study treatment is 90 days, with the primary efficacy assessment at Day 90. Safety and efficacy evaluations will be conducted at Days 14 (±3 days), 28 (±3 days), 42 (±3 days), 60 (±3 days), and 90 (±3 days).

4 STUDY POPULATION SELECTION

4.1 Study Population

Male or female subjects ≥2 years of age with a diagnosis of dry eye disease will be included in this study. Please see Sections 4.2 and 4.3 for specific inclusion and exclusion criteria, respectively. Approximately 195 evaluable subjects will be enrolled at approximately 20 clinical sites in the United States.

4.2 Inclusion Criteria

Subjects who meet the following criteria will be included in the study:

1. Subjects ≥2 years of age
2. Documented medical history of dry eye disease for a period of at least 6 months
3. Use of artificial tears for at least 3 months prior to screening
4. BCVA better than 20/400 in both eyes
5. Provision of signed, written consent prior to participation in any study-related procedures; or signed written consent from parent or legal guardian if the subject is a minor and signed written assent from minor subject, if appropriate

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Previous use of CSA 0.05% (Restasis®) within the 3 months prior to screening
2. Previous treatment failure on CSA 0.05% (Restasis®)
3. Current use of systemic cyclosporine
4. Systemic and topical ophthalmic medications that are known to cause dry eye disease are prohibited and must not have been taken within 7 days of screening. These include the following medications:
   - Immunomodulators (permitted if dose is stable for 3 months prior to screening and not expected to change during the study period)
   - General anesthetics
   - Antihistamines (including over-the counter [OTC])
   - Cholinergics
   - Antimuscarinics
   - Tricyclic antidepressants
   - Phenothiazines
5. Any topical ophthalmic medications other than the assigned study medication or the provided artificial tears (Refresh Plus®)
6. Current active eye disease, other than dry eye disease (ie, any disease for which topical ophthalmic medication is necessary)
7. Abnormal lid position or closure in both eyes
8. End-stage lacrimal disease (Schirmer test score with nasal stimulation of <3 mm/5 min) or dry eye disease as the result of destruction of conjunctival goblet cells or scarring

9. Presence or anticipated use of punctal occlusion in the study eye
10. Intraocular or refractive surgery (including cataract extraction, LASIK, vitrectomy, or trabeculectomy) in the study eye within 3 months prior to study start
11. Unwilling to discontinue use of contact lenses during the duration of the study
12. Pregnancy or lactation, confirmed by urine pregnancy test. The test will be conducted if the Investigator deems it necessary.
13. Presence or history of any systemic or ocular disorder or condition that could possibly interfere with the interpretation of the study results in the study eye
14. HIV positive or diagnosis of AIDS
15. Known hypersensitivity to any component of the study or procedural medications
16. Participation in any other clinical trial within 30 days prior to screening
17. Unable to reliably report symptoms and history

5 TRIAL TREATMENT(S)

5.1 Description of Treatments

Treatment with the study drug will be for 90 days, from Day 0 to Day 90 inclusive.

5.1.1 Study Drug

CSA 0.1% and CSA 0.2% will be supplied by Sirion Therapeutics, as a 5 mL fill in a 6 cc LDPE bottle and is a multidose sterile solution.

5.1.2 Vehicle

The vehicle will be supplied by Sirion Therapeutics in a container-closure system identical to the study drug.

5.2 Treatments Administered

Subjects who meet inclusion criteria at baseline (Day 0) will be randomized to 1 of 3 treatment groups:

Treatment Group 1: Approximately 65 subjects will receive 1 drop of CSA 0.1% per eye 2 times per day (BID) for 90 days

Treatment Group 2: Approximately 65 subjects will receive 1 drop of CSA 0.2% per eye BID for 90 days

Treatment Group 3: Approximately 65 subjects will receive 1 drop of vehicle per eye BID for 90 days

5.3 Selection and Timing of Dose for Each Subject

All subjects will self-administer the allocated treatment. Subjects will be instructed to administer a dose in the morning and a dose in the evening, with approximately 12 hours between doses.

5.4 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned 1:1:1 to receive CSA 0.1%, CSA 0.2%, or vehicle. Randomization will be conducted by assigning each eligible subject a number that corresponds to a block randomization list generated by an independent statistician. The vendor responsible for packaging and shipping the study drug will be responsible for maintaining trial treatment randomization codes. Randomization will be assigned online via electronic data capture software. Emergency codes will be available via a toll-free number manned continuously throughout the trial period.

5.5 Masking

This study is double-masked; all clinical site personnel, the subject, and Sirion Therapeutics personnel will be masked to treatment allocation. The investigational products will be indistinguishable from each other in packaging appearance. The vendor responsible for packaging and shipping the study drug will be responsible for maintaining the randomization codes.

5.5.1 Unmasking During the Study Period

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the Iinvestigator should follow the procedure outlined below. The randomization 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. In the event of emergency or life-threatening condition, the Investigator may need to unmask the subject.

The following procedure should be followed:

1. The Investigator should contact Sirion Therapeutics immediately before unmasking a subject unless it is not possible to do so without risk to the subject. If the cannot contact the Medical Monitor and the situation is an emergency, the clinical trial material labeler should be contacted. The contact number can be found on the label of the clinical trial material as well as provided with the clinical trial material shipments.
2. The Investigator should document the adverse event (AE) or serious AE (SAE) and justification for unmasking in the eCRF. This information should be noted in the relevant AE or SAE eCRF form.
3. The subject may continue to participate in the study at the Investigator's discretion. If the subject is withdrawn from study treatment prematurely, all of the measures should be performed as soon as possible following the final dose of study drug providing the subject has not withdrawn consent and recorded on the appropriate eCRF.
4. The Investigator should contact Sirion Therapeutics within 24 hours with the randomization number, subject initials, details of the AE or SAE, any action taken, and whether the subject is continuing in the study.

5.6 Concomitant Medications

Artificial tears (Refresh Plus®) will be dispensed to subjects for use during the treatment period. **Subjects will be instructed to use the artificial tears only <u>as needed</u> up to 8 times per day. Subjects also will be instructed not to use the artificial tears within 30 minutes of instilling the study drug.** All other artificial tear products, including any topical ophthalmic medications other than the assigned study medication, must be discontinued from screening through Day 90.

Subjects will be excluded from the trial if they are receiving concurrent systemic cyclosporine. Additionally, systemic and topical ophthalmic medications that are known to

cause dry eye disease are prohibited and must not have been taken within 7 days of screening. These include the following medications:

- Immunomodulators (permitted if dose is stable for 3 months prior to screening and not expected to change during the study period)
- General anesthetics
- Antihistamines (including OTC)
- Cholinergics
- Antimuscarinics
- Tricyclic antidepressants
- Phenothiazines

5.6.1 Prior Therapies

Certain prior therapies will not be allowed:

- Current systemic use of cyclosporine
- Topical CSA 0.05% (Restasis) within 3 months prior to screening.
- Presence of punctal occlusion (permanent or temporary)
- Intraocular or refractive surgery (including cataract extraction, LASIK, vitrectomy, or trabeculectomy) in the study eye within 3 months prior to study start

5.7 Treatment Compliance

Subjects will self-administer the study drug during the treatment period. The importance of compliance with the dosing schedule should be stressed to the subject. Subjects will be asked about their medication administration at the Day 14, 28, 42, 60, and 90 study visits.

5.8 Packaging and Labeling

CSA 0.1%, CSA 0.2%, and vehicle will be packaged in identical bottles. Artificial tears (Refresh Plus) will be provided in the commercial packaging.

5.9 Storage and Accountability

The study drugs should be stored at room temperature, 20°C to 25°C (68°F to 77°F), in the original packaging. The subjects should maintain study medications at room temperature at all times, and return all study medications at the last study visit (Day 90).

Upon receipt of the study drug supplies, an inventory must be conducted as soon as possible. Sites will record the number of bottles received and the number assignment printed on each bottle in the Drug Accountability section of the eCRF. A copy of the drug receipt form must be kept in a secured location at the site. During the trial, the site must account for all investigational drug product additions, usage, discrepancies, or deficiencies on the Drug Accountability section of the eCRF. All supplies must be accounted for at the conclusion of the study; therefore, no used or partially used supplies should be discarded. Subjects should

be requested to return all used or unused study medication. Any accidental or deliberate destruction of the investigational drug products should be documented on the Comments page of the eCRF.

During the study close-out process, the clinical monitor and site personnel will work together to inventory all supplies on a drug-return form. All used and unused study drug products must be returned by a traceable method to the vendor designated by Sirion Therapeutics. A copy of the drug return form must be kept in a secured location at the clinical site.

5.10 Investigational Product Retention at Study Site

All investigational drug products supplied to the Investigator must be accounted for in this study. Study medication must be kept in a secured location, and all medication should be returned to the study site and retained until the study close-out.

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 IRB-approved version of the informed consent form. In the case of a minor subject, fully informed consent must be obtained from the parent/legal guardian in accordance with local legal requirements and IRB requirements. Where appropriate, minor study subjects should assent to enroll in this study (with age of assent to be determined by the IRB and be consistent with local legal requirements). The original informed consent form is to be retained by the study site, and a copy is to be given to the subject. Section 10.3 provides details of the administration of subject information and consent.

6.2 Medical History

A complete medical history, including previous or current diseases or illness, will be obtained at the baseline visit. A complete surgical history should also be documented.

The ocular history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures).

A urine pregnancy test will be administered at entry if the Investigator determines this is necessary.

6.3 Dispensing Study Drug

A supply of study drug or vehicle, as allocated, will be provided to each subject who meets inclusion/exclusion criteria at baseline. Subjects will be instructed to administer 1 drop per eye of study medication BID. The first dose will be administered by the subject under study personnel supervision; subjects will self-administer treatment for the remainder of the trial. To facilitate drug accountability and compliance, subjects will be instructed to return used, emptied containers at each subsequent study visit. Subjects will also be instructed to return all remaining containers, used or unused.

Artificial tears (Refresh Plus®) will be dispensed to subjects for use during the treatment period. **Subjects will be instructed to use the artificial tears only as needed up to 8 times per day. Subjects also will be instructed not to use the artificial tears within 30 minutes of instilling the study drug.** All other artificial tear products, including any topical ophthalmic medications other than the assigned study medication, must be discontinued from screening/baseline through Day 90. Subjects will be instructed to return used, emptied containers at each subsequent study visit. Subjects will also be instructed to return all remaining containers, used or unused, on Day 90

6.4 Efficacy Assessments

Efficacy will be assessed using objective (lissamine green staining, corneal fluorescein staining, and Schirmer test) and subjective (symptom frequency rating and symptom intensity rating) measures in both eyes.

6.4.1 Objective Efficacy Parameters

6.4.1.1 Lissamine Green Staining of the Cornea and Conjunctiva

Corneal and conjunctival staining will be performed in both eyes using 1 drop of 1% lissamine green solution, with results observed in low to moderate intensity white light of the slit lamp between 1 and 4 minutes following instillation. The areas evaluated will be the cornea and the nasal and temporal conjunctiva. Each area will be graded as follows:

- 0 = 0%
- 1 = 1%–15%
- 2 = 16%–30%
- 3 = 31%–45%
- 4 = >45%

The Investigator will record a score for each area (cornea, nasal conjunctiva, and temporal conjunctiva) of each eye. The scores for each eye will be summed. Lissamine green staining will be performed at all study visits.

6.4.1.2 Corneal Fluorescein Staining

Fluorescein staining of the corneal epithelium will be performed in both eyes at all study visits. Dye will be placed in the eye using blotting paper impregnated with fluorescein dye moistened with a full single drop (must be at least 10 µL) of balanced salt solution (BSS). The subject will be asked to blink several times in order to disperse the dye uniformly. The cornea will be examined 3 minutes after instillation using the cobalt blue filter of the slit lamp and a Wratten #12 yellow filter to view the surface of the eye and identify abnormalities where staining appears.

Corneal Stain Intensity

Regarding corneal stain intensity scores, 5 specific areas of the cornea will be identified: area 1=central (defined as the central 5 mm of the cornea), area 2=temporal, area 3=inferior, area 4=nasal, and area 5=superior. Fluorescein staining of each corneal area will be graded on a 0-3 scale:

0=No staining
1=Mild staining
2=Moderate staining
3=Severe staining

To evaluate for central corneal clearing, the Investigator will record the corneal stain intensity score for area 1 (central).

The Investigator will also record scores for areas 2, 3, 4, and 5. The scores for areas **1-4 only (central, temporal, inferior, and nasal)** will be summed to tabulate a total score per eye for corneal stain intensity.

Corneal Stain Summed Score

To achieve a summed score in corneal fluorescein staining, each of 3 characteristics (ie, type, extent/surface area, depth) will be graded on a 0-4 scale:

5. Type
   - 0 = No staining
   - 1 = 2-5 areas of punctate staining
   - 2 = >5 up to 15 areas of punctate staining or 1 area of coalesced staining
   - 3 = >15 areas of punctate staining or 2 or more areas of coalesced staining or any area of epithielial or stromal diffusion of fluorescein
   - 4 = >15 areas of punctate staining and 2 or more areas of coalesced staining and a frank corneal epithelial defect

6. Extent/Surface Area
   - 0 = 0%
   - 1 = 1%–15%
   - 2 = 16%–30%
   - 3 = 31%–45%
   - 4 = > 45%

7. Depth
   - 0 = No staining
   - 1 = Superficial epithelium
   - 2 = Deep epithelium, delayed stromal glow
   - 3 = Immediate localized stromal glow
   - 4 = Immediate diffuse stromal glow

The Investigator will record the score for each characteristic (type, extent/surface area, and depth). These scores will be used to tabulate a summed score per eye for corneal fluorescein staining.

6.4.1.3 Schirmer Test

The Schirmer test will be performed in both eyes with anesthesia for all study visits. The subject should be sitting comfortably in a room without extremely bright lighting. Two drops of topical anesthetic will be instilled into each eye 2 minutes before insertion of the Schirmer strips. The eye should be lightly blotted with tissues to remove excess anesthetic or tears. The

filter paper strips will be placed at the junction of the middle and lateral 1/3 of the lower eyelid, avoiding contact with the cornea. Strips should be placed in both eyes at the same time and timed for 5 minutes. The subject may sit with their eyes gently closed during this period and should avoid excessive blinking during the test. Strips will be removed after 5 minutes and the amount of wetting is recorded in millimeters (mm). The subject should be reminded not to rub his/her eyes for at least 30 minutes after the completion of the test.

6.4.2 Subjective Efficacy Parameters

6.4.2.1 Symptom Frequency

Symptom frequency will be assessed at all study visits, according to the following rating scale, for 7 symptoms: burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation:

0 = Never
1 = Sometimes
2 = Often
3 = Constantly

The subject will rate each of the 7 dry eye symptoms using the scale and each symptom score will be recorded by the Investigator. These scores will be summed to arrive at a total symptom frequency score.

6.4.2.2 Symptom Intensity

The Visual Analogue Scale (VAS) will be used at all study visits to assess the presence and severity of dry eye symptoms: burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation on a 0-100 mm scale (0 = absent and 100 = severe). The subject marks the point on the scale that best depicts each symptom, and the distance between the 0 point and the subject's mark is measured in mm and recorded by study personnel.

6.5 Safety Assessments

Safety will be assessed using objective (BCVA, slit lamp examination, ophthalmoscopy, and IOP measurement) and subjective (subject comfort and tolerability) measures in both eyes, unless otherwise specified.

6.5.1 Best-Corrected Visual Acuity

BCVA measurement will be performed at all study visits with the Snellen eye chart (using the subject's current corrective lens prescription) at a distance of 20 feet (6 meters).

6.5.2 Slit Lamp Examination

A routine slit lamp examination will be performed at all study visits to evaluate the anterior segment of the eye, including lids, cornea, sclera, conjunctiva, lid margins, lens, and capsule. Abnormalities will be documented.

6.5.3 Ophthalmoscopy

Direct ophthalmoscopy will be performed at baseline and at Day 90.

6.5.4 Intraocular Pressure

All IOP measurements will be performed utilizing Goldmann applanation tonometry using standard of care. To avoid changes due to the diurnal rhythm, the IOP in a given subject should be recorded at approximately the same time of day throughout the study. IOP measurement will be conducted at baseline, and Days 28 and 90.

6.5.5 Subject Comfort and Tolerability

An evaluation of subject comfort following the first (Day 0) and last (Day 90) instillations of the study medication will be performed. Subjects will rate their experience of burning, stinging, and blurring of vision following instillation of study drug using the following scale:

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

6.6 Adverse Events Assessments

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

6.6.1 Performing Adverse Events Assessments

AEs will be assessed by the Investigator at each study visit, once subjects receive the first dose of study drug. The first dose of study medication will be administered by the subject under study site personnel supervision and the **subjects will be observed for any AEs over the ensuing 30 minutes.** Any and all abnormalities seen by physical, ocular, and ophthalmic examination will be noted.

To further elicit AEs, simple questions with minimal connotations will be used as the initial questions at all evaluation points during the trial.

For example:

- How do your eyes feel?
- Have you had any health problems since your last assessment?

The AE probe will be conducted by the same study personnel for each visit for an individual subject, if at all possible.

All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded using standard medical terminology. The onset, duration, severity, action taken, relationship to treatment, and outcome of all AEs will be documented in the eCRF. The Investigator must assess (and record in the eCRF) the degree to which the event was related to the study medication. Subjects with an AE should be carefully followed to determine outcome until resolution or 30 days after the last study visit, whichever comes first. If no AE has occurred, this should be noted in the appropriate place on the AE section of the eCRF.

6.6.2 Timing

Any AE that begins on or after baseline (Day 0) following the initial dose of study medication until the end of the treatment period (Day 90) is to be recorded in the appropriate section of the eCRF. Subjects with an AE should be carefully followed to determine outcome until resolution or 30 days after the last study visit, whichever comes first.

6.6.3 Severity

The Investigator will use the following definitions to code the intensity of the event:

- **Mild** Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities
- **Moderate** Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually relieved by simple therapeutic measures
- **Severe** Causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment

There is a distinction between the severity and the seriousness of an AE. Severe is a measurement of intensity; thus, a severe reaction is not necessarily an SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs listed in Section 6.6.7.1.

6.6.4 Relationship

The relationship or association of the study medication to an AE, as causing or contributing to the AE, will be characterized as defined below:

- **Not related** Evidence indicates no plausible direct relationship to the study medication
- **Unlikely related** Suggests other conditions are reasonably likely to account for the event including concurrent illness, progression, or expression of the disease state, or reaction to concurrent medication
- **Possibly related** Suggests that the association of the event with the study medication is unknown; however, the AE is not reasonably supported by other conditions
- **Related** Follows anticipated response to study medication and is confirmed by discontinuing and/or rechallenge

Procedures such as surgery should not be recorded as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of AE as described previously.

6.6.5 Expectedness

In a previous clinical trial where CSA concentrations ranged from 0.1% to 0.4% in the treatment of moderate-to-severe dry eye, AEs were uncommon and no significant AEs were reported (Stevenson, 2000).

In more recent studies by Sirion Therapeutics comparing CSA 0.1% to vehicle in treating moderate-to-severe dry eye, the AE's reported most frequently among both the CSA-treated and vehicle-treated subjects were as follows: eye irritation, conjunctival hyperaemia, ocular hyperaemia, dry eye, and foreign body sensation in eyes (Data on File, 2008).

Unexpected AEs are defined as any AE, the specificity or severity of which is not consistent with the current Investigator's Brochure.

6.6.6 Clinical Significance

The medical monitor, in consultation with the Investigator, will be responsible for determining whether an AE is clinically significant for the subject or the study overall.

6.6.7 Serious Adverse Events

6.6.7.1 Definition

An SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.6.7.2 Reporting Serious Adverse Events

To report an SAE, complete the online eCRF within 24 hours of the Investigator being notified of the event.

Specific medical questions can be addressed to the medical monitor.

Roger Vogel, MD, Medical Monitor
813-496-7325, ext. 228 (office)
941-349-9771 (after hours)
941-284-4034 (mobile)
813-496-7324 (fax)
E-mail: rogervogel@aol.com

All follow-up information to SAEs should be provided to Sirion Therapeutics within 3 calendar days of receipt at the site.

The Investigator must notify the approving IRB of any SAEs regardless of cause within 24 hours. Sirion Therapeutics will be responsible for reporting SAEs to the FDA.

6.7 Concomitant Medication Documentation

Concomitant medications should be reviewed upon arrival at each study visit for any changes since the last visit. Changes and the reason for the change should be recorded on the Concomitant Medication form of the eCRF.

6.8 Removal of Subjects From the Trial or Study Drug

In the event that it is judged by the Investigator that the subject should be withdrawn from the trial and after discussion with the medical monitor, then the subject should be withdrawn and treated at the discretion of the Investigator. The last measured values on the efficacy measures will be carried forward from that point.

The Investigator may withdraw a subject from study treatment for any of the following reasons:

- The subject withdraws consent
- The Investigator believes that continuation in the trial is contrary to the subject's best interests
- A protocol violation occurs
- The subject is lost to follow-up
- A serious or intolerable AE occurs
- The sponsor or Investigator terminates the study

If the subject is withdrawn from study treatment prematurely, providing the subject has not withdrawn consent, all of the Day 90 measures (Section 6.2.5) should be performed as soon as possible following the final dose of study drug. If the subject is lost to follow-up, 2 documented attempts should be made to contact the subject to return for a final evaluation. If it is necessary for the subject to attend the clinical site for an unscheduled visit, the appropriate observations/evaluations will be performed and recorded on the applicable eCRF page.

6.9 Appropriateness of Measurements

All of the measurements used in this study are standard, recognized methods of assessing the safety and tolerability of ophthalmic products and are commonly employed in clinical trials in the area of ophthalmology.