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Clinical Study SY201-CS201

Protocol

13 April 2022

Title Page

A Phase 2, Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Dose-Response, Parallel-Group Study of SY-201 Ophthalmic Solution versus Vehicle Control in Subjects with Dry Eye Disease

Protocol No:	SY201-CS201
National Clinical Trial No.:	Pending
Study Phase:	2
Sponsor:	Seinda Pharmaceutical Guangzhou Corp. C401, No. 9 Luoxuan 4th Road Guangzhou International Bio-island Guangzhou, Guangdong, China, 510300
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Protocol Revision History

Protocol Synopsis

Title:	A Phase 2, Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Dose-Response, Parallel-Group Study of SY-201 Ophthalmic Solution versus Vehicle Control in Subjects with Dry Eye Disease
Phase:	2
Design/Conduct:	This is a phase 2, multi-center, double-masked, randomized, vehicle-controlled, dose-response, parallel-group study designed to evaluate the ocular and systemic safety and ocular efficacy of SY-201 Ophthalmic Solution over a 60-day treatment period in subjects with moderate to severe DED. During the 14-day single-masked run-in period, approximately 200 subjects will instill vehicle as 1 drop in both eyes (OU) twice a day (BID). At Visit 2, subjects will be randomized in a 1:1:1:1 ratio to 4 treatment groups: Vehicle (n=50) and SY-201 Ophthalmic Solution 2.0% (n=50), 1.0% (n=50), and 0.5% (n=50). Double-masked IP will be instilled as 1 drop OU BID for 60 days. The study will consist of 6 clinic visits: Visit 1 (-14 Days, Screening), Visit 2 (Day 1, Randomization), Visit 3 (Day 7 ± 2 days), Visit 4 (Day 14 ± 2 days), Visit 5 (Day 28 ± 2 days), and Visit 6 (Day 60 ± 3 days, End of Study/Early Termination).
Objectives:	The primary objective is to assess the ocular safety and efficacy of SY-201 Ophthalmic Solution in subjects with DED. The secondary objective is to assess the systemic safety of SY-201 Ophthalmic Solution in subjects with DED.
Endpoints:	<u>Primary Efficacy Endpoints</u> Two primary ocular efficacy endpoints (one sign and one symptom) will be tested sequentially: • Mean change from baseline (CFB) in total corneal fluorescein staining (tCFS; modified National Eye Institute [mNEI] scale, 0-20) [redacted] <u>Safety Endpoints</u> The ocular and systemic safety of SY-201 Ophthalmic Solution will be assessed by: • Frequency and severity of ocular and non-ocular adverse events (AEs) • Serum chemistry and hematology • Best corrected visual acuity (BCVA)

	• Slit lamp biomicroscopy and external eye exam • Intraocular pressure (IOP) • Dilated ophthalmoscopy • Drop comfort assessment
Population studied:	The study population will consist of approximately 200 adult subjects with moderate to severe DED. The study eye is defined as the eye meeting all inclusion criteria and no exclusion criteria, and with the highest tCFS scoring at randomization (Visit 2, Day 1). If both eyes meet the inclusion criteria and no exclusion criteria and have the same tCFS score, the right eye will be used as the SE. <u>Inclusion Criteria</u> Individuals will be eligible for study participation if they meet all of the following criteria: 1. Provide written informed consent prior to any study-related procedures. 2. Are 18 years of age or older. 3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study. 4. Have a BCVA in each eye, using corrective lenses if necessary, of +0.7 logarithm of the minimum angle of resolution (LogMAR) or better as assessed by the Early Treatment of Diabetic Retinopathy Study (ETDRS) at Visit 1. 5. If women of childbearing potential (WOCBP), are non-lactating and have been sexually inactive (abstinent) for 14 days prior to Visit 1 and remain so through 30 days following Visit 6 or the last administration of the study drug or until completion of the subject's first menstrual cycle following the last administration of the study drug, whichever period of time is longer. Or they must have been using one of the following acceptable methods of birth control for the times specified: a. Intra-uterine device (IUD) in place for at least 3 months prior to Visit 1 through 30 days following Visit 6 or last administration of study drug or until completion of the subject's first menstrual cycle following last administration of the study drug, whichever period of time is longer. b. Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to Visit 1 through 30 days following Visit 6 or last administration of the study drug or until completion of the subject's first menstrual cycle following last administration of the study drug, whichever period of time is longer. c. Stable hormonal contraceptive for at least 3 months prior to Visit 1 through 30 days following Visit 6 or last administration of the study drug or until completion of the subject's first menstrual cycle following administration of the study drug, whichever period of time is longer. Note: For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following administration of the study drug is not applicable, as females receiving this form of contraception will not have menses. d. Surgical sterilization (vasectomy) of partner at least 6 months prior to Visit 1.

	6. If postmenopausal women, have had no menstrual cycle for at least 1 year prior to Visit 1 or have undergone one of the following sterilization procedures at least 6 months prior to Visit 1: a. Bilateral tubal ligation b. Hysterectomy c. Bilateral oophorectomy 7. Have a history of DED in both eyes supported by a previous clinical diagnosis or have a history of subjective complaints for at least 6 months rior to Visit 1. [redacted] 10. Have normal lid anatomy in the opinion of the investigator. 11. Are willing to withhold AT for the duration of the study, with the exception of rescue use of the study-provided AT (Refresh Plus®). <u>Exclusion Criteria</u> Individuals will be excluded from study participation if they meet any of the followin criteria: 2. Any concomitant treatment or prior ocular procedure or surgery in either eye or alteration of the dose of systemic medications at the time of entry into the study that could interfere in the assessment of the trial, per the Investigator's judgment or per details below: a. Prior history of Isotretinoin (Accutane) b. Corneal refractive surgery, glaucoma surgery, or corneal transplantation within 2 years prior to Visit 1 c. Altered use of nutraceuticals or multivitamins throughout the study d. Topical ophthalmic medications, including ocular hypotensive (glaucoma) medications, eye drops, gels, or AT (other than study-provided Refresh Plus®) throughout the study f. Penetrating intraocular surgery within 12 months prior to Visit 1 g. Eyelid surgery or ocular surface surgery within 6 months prior to Visit 1 h. Altered dose of the following used on a chronic basis within 3 months prior to Visit 1: • Anticholinergics • Antidepressants • Antihistamines • Systemic immunosuppressive agents

- Oral steroids (dose must be <11 mg prednisone or equivalent/day)

  Dose must remain stable throughout study.

i. In either eye, have had punctal occlusion (cauterization or plugs [silicone or dissolvable]) within 3 months prior to Visit 1 or anticipate new or additional punctal occlusion during the duration of the study.

   NOTE: Permanent plugs lost should be replaced.

j. Any other Investigational Product within 45 days prior to Visit 1

k. Prescription treatments for ocular surface disease within 30 days prior to Visit 1, including

- Topical cyclosporine (Restasis®, Cequa®)
- Topical lifitegrast (Xiidra®)
- Ocular corticosteroids, including but not limited to fluorometholone and loteprednol etabonate (Eysuvis®)
- Varenicline (Tyvara®)

l. Autologous serum within 30 days prior to Visit 1

m. Altered dose of tetracycline compounds (tetracycline, doxycycline, or minocycline) within 30 days prior to Visit 1.

   Dose must remain stable throughout study.

n. Topical ocular antibiotics, topical ocular antihistamines or mast cell stabilizers, topical or nasal vasoconstrictors within 14 days prior to Visit 1

3. Have corneal erosive disease (e.g., confluent staining [NEI grade 4], confluent filaments) or other conditions suggestive of extensive damage of the cornea in either eye.
4. Have a history of glaucoma or IOP >25 mmHg at Visit 1 or a history of elevated IOP (>25 mmHg) in either eye.
5. Wear contact lenses for 14 days prior to Visit 1 or throughout the study.

[redacted]

7. Are considered legally blind in either eye (LogMAR BCVA ≥1.0 or Snellen BCVA ≤20/200).

[redacted]

9. Have a history of stem cell or bone marrow transplant.

[redacted]

	[redacted] g. Significant conjunctival scarring h. Chemical burn i. History of herpetic or neurotrophic keratitis j. Serious systemic disease or uncontrolled medical condition that, in the judgment of the Investigator, could confound study assessments or limit compliance. 11. Have a history of liver, renal or hematological disease that, in the judgment of the Investigator, could confound the study assessments or impact subject safety. 12. Have an allergy to any component of the study drug formulation. 13. Have a documented history of ocular allergies in either eye that, in the judgment of the Investigator, are likely to have an acute increase in severity due to the expected timing of the exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted. 14. Have systemic signs of infection (e.g., fever or current treatment with antibiotics). 15. Are an employee of a site that is directly involved in the management, administration, or support of this study or an immediate family member (grandparent, parent, sibling, child) of the same. 16. Have a known history of alcohol and/or drug abuse. 17. Are an active dail user of tobacco or mari uana. [redacted] 19. Are unwilling or unable to comply with the study protocol.
Investigational products:	SY-201 Ophthalmic Solution 2.0% SY-201 Ophthalmic Solution 1.0% SY-201 Ophthalmic Solution 0.5% Vehicle solution (run-in and vehicle)
Dosing regimen:	Both run-in and IP: 1 drop OU BID, once in the morning and once in the evening, 8-12 hours apart
Assessments/Evaluations:	<u>Efficacy</u> • tCFS (mNEI scale, 0-20) [redacted]

	Safety • AE monitoring • Safety labs (chemistry and hematology) • BCVA • Slit lamp biomicroscopy and external eye exam • IOP • Dilated ophthalmoscopy • Drop comfort assessment
Duration of study:	74 days (14 days of run-in, 60 days of treatment)
Statistical methods:	For mean change from baseline to Day 60 in tCFS, a sample size of 45 SY-201–treated subjects versus 45 vehicle-treated subjects will have 87.9% power to detect an effect size of 2.0 units with a standard deviation of 3.0 for an unpaired t-test with a 2-sided al ha = 0.05. For mean change from baseline to Day 60 in dry eye symptom a sample size of 45 SY-201–treated subjects versus 45 vehicle-treated subjects will have 83.5% power to detect an effect size of 1.5 units with a standard deviation of 2.4 for an unpaired t-test with a 2-sided alpha = 0.05. Fifty (50) subjects per treatment arm, for a total 200 subjects, will be enrolled to allow for some dropout of subjects. It is hypothesized that SY-201 Ophthalmic Solution will be safe and improve DED signs and symptoms in subjects with a documented diagnosis of DED. In particular, efficacy will be assessed using the following endpoints at Day 60: • Mean CFB in tCFS (mNEI scale) [redacted] To control for type I error, comparisons will be made within each active dose level of SY-201 Ophthalmic Solution compared to vehicle. In other words, the primary endpoints will be compared sequentially between SY-201 Ophthalmic Solution 2.0% and vehicle, first testing tCFS and, if statistically significant, then Should both endpoints achieve statistical significance for the 2.0% dose, testing will proceed to SY-201 Ophthalmic Solution 1.0% versus vehicle, first testing tCFS and, if statistically significant, then . Should both endpoints achieve statistical significance for the 1.0% dose, testing will proceed to SY-201 Ophthalmic Solution 0.5% and vehicle, first testing tCFS and, if statistically significant, then In other words, the first non-significant result in this testing hierarchy of six hypotheses will imply that subsequent tests are non-significant. Mean CFB in tCFS will be analyzed using a mixed-model repeated measures (MMRM) model. The model will include the baseline measurement, treatment, time, and treatment by time interaction as fixed effects, with a random effect for site. An unstructured covariance among repeated measurements is assumed. A similar model for the subject-level mean CFB in eye dryness score will be used. [redacted]

	Subgroup analyses will be based on MMP-9 level (elevated or normal) in the study eye at baseline. Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular AEs, laboratory measurements, BCVA, IOP, ophthalmic exams using slit lamp biomicroscopy and dilated ophthalmoscopy, and drop comfort assessment. Summaries will be provided by treatment group, and for ocular assessments separately by eye.

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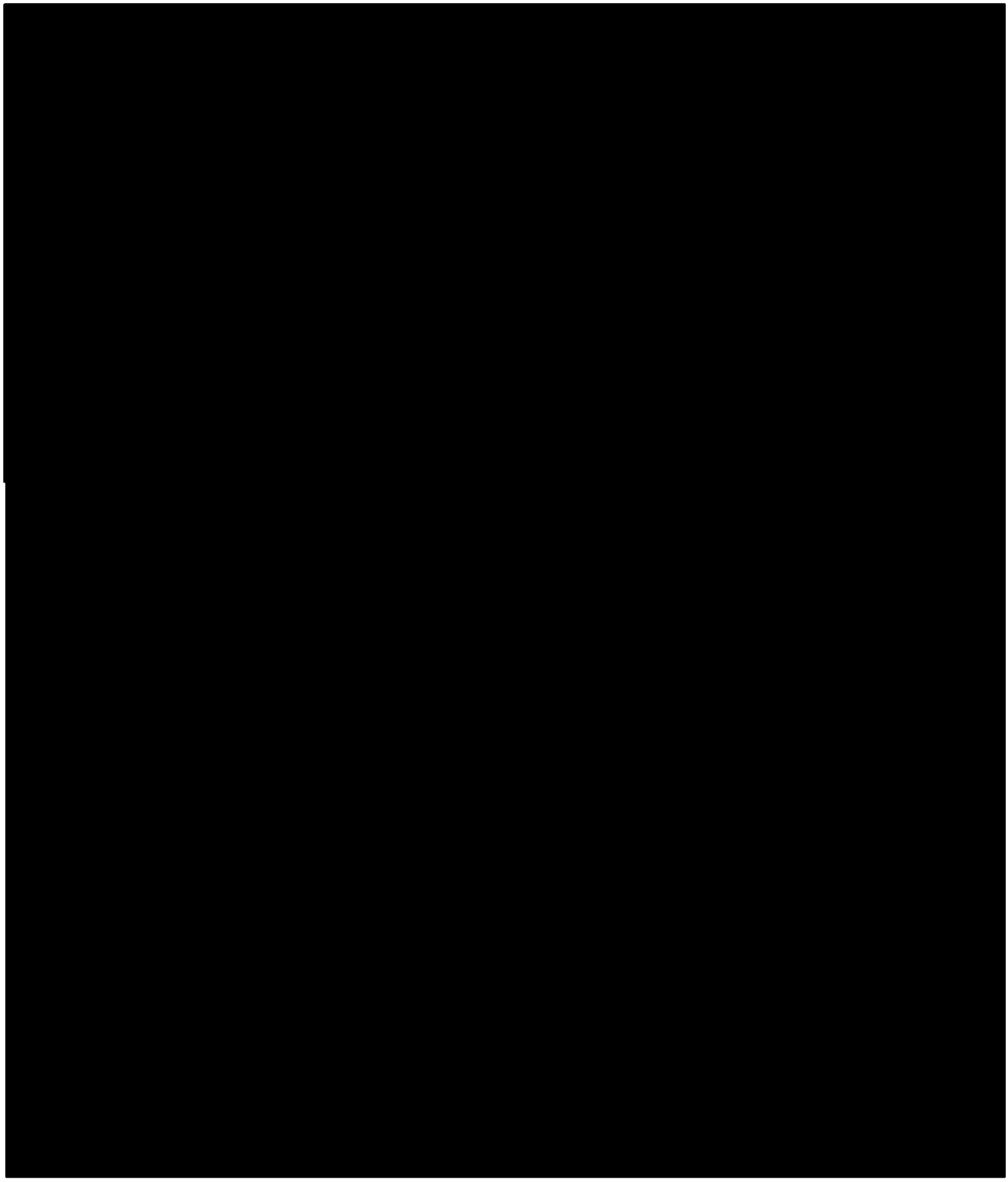
1. Introduction

1.1 Background



1.2 Study Rationale

Global prevalence of DED is estimated at 300 million, or 5% to 50% of select populations, with the disease generally more common in women than men and in Asian populations compared to Caucasian populations (Stapleton et al., 2017).

Current treatments for DED include tear replacement, anti-inflammatory agents, serum or umbilical cord serum eye drops, and surgical interventions. According to Jones (2017), it is "clear that many of the treatments available for the management of dry eye disease lack the necessary Level 1 evidence to support their recommendation" and there are "challenges . . . in predicting the relative benefits of specific management options." Approved topical treatments have been associated with side effects such as instillation pain and irritation (Schultz 2014, Leonardi 2016), ocular hypertension, and cataract formation (Marsh 1999).

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

[redacted]

1.3.2 Known Potential Benefits

1.3.3 Assessment of Benefits and Risks

2. Study Objectives and Endpoints

2.1 Study Objectives

The **primary objective** of this phase 2 study is to assess the ocular safety and efficacy of SY-201 Ophthalmic Solution in subjects with DED.

The **secondary objective** is to assess the systemic safety of SY-201 Ophthalmic Solution in subjects with DED.

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoints

Two primary ocular efficacy endpoints (one sign and one symptom) will be tested sequentially at Day 60:

- Mean change from baseline (CFB) in total corneal fluorescein staining (tCFS; modified National Eye Institute [mNEI] scale, 0-20)

[redacted]

2.2.2 Secondary Efficacy Endpoints

The following secondary ocular efficacy endpoints will be tested:

[redacted]

2.2.3 Safety Endpoints

The ocular and systemic safety of SY-201 Ophthalmic Solution will be assessed by:

- Frequency and severity of ocular and non-ocular adverse events (AEs)
- Serum chemistry and hematology
- Best corrected visual acuity (BCVA)
- Slit lamp biomicroscopy and external eye exam

- Intraocular pressure (IOP)
- Dilated ophthalmoscopy
- Drop comfort assessment

3. Study Design

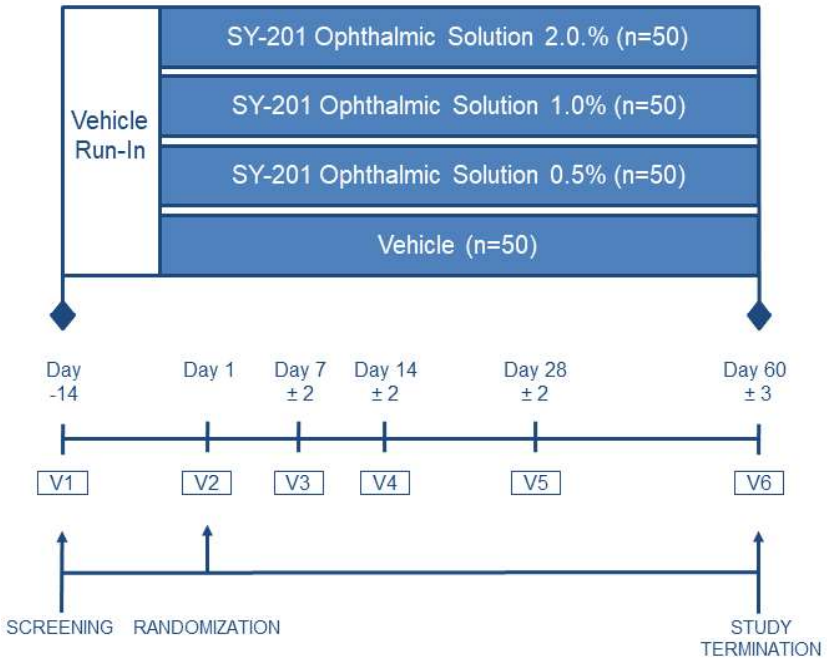
3.1 Overall Design of the Study

This is a phase 2, multi-center, double-masked, randomized, vehicle-controlled, dose-response, parallel-group study designed to evaluate the ocular and systemic safety and ocular efficacy of SY-201 Ophthalmic Solution over a 60-day treatment period in subjects with moderate to severe DED.

During the 14-day single-masked run-in period, approximately 200 subjects will instill vehicle as 1 drop BID in both eyes (OU). At Visit 2, subjects will be randomized in a 1:1:1:1 ratio to 4 treatment groups: Vehicle (n=50) and SY-201 Ophthalmic Solution 2.0% (n=50), 1.0% (n=50), and 0.5% (n=50). Double-masked IP will be instilled as 1 drop OU BID for 60 days.

The study will consist of 6 clinic visits: Visit 1 (-14 Days, Screening), Visit 2 (Day 1, Randomization), Visit 3 (Day 7 ± 2 days), Visit 4 (Day 14 ± 2 days), Visit 5 (Day 28 ± 2 days), and Visit 6 (Day 60 ± 3 days, End of Study/Early Termination). A study schematic follows (Figure 1).

Figure 1: Study Schematic



3.2 Rationale for the Study Design

This study will examine the ocular and systemic safety and ocular efficacy of SY-201 Ophthalmic Solution versus vehicle dosed OU BID for 60 days in subjects with moderate to severe DED.

SY-201 Ophthalmic Solution and vehicle will each be administered as a topical ophthalmic solution. In the single-masked run-in period, vehicle will be dosed OU BID by all subjects to normalize baseline conditions between subjects. Subjects will self-administer the first dose in-clinic at Visit 1 and all remaining doses at home. In the double-masked treatment period, subjects will self-administer 1 dose of IP in-clinic at Visit 2 (Day 1) and Visit 6 (Day 60) and all remaining doses at home, OU BID.

Direct instillation is the most efficient method for delivery to the ocular surface and is an accepted and widely used method for topical application to the eye. Each dose will be delivered by administering 1 drop (in each eye from a single-use vial.

3.3 Dose Justification

The concentrations of 2.0%, 1.0%, and 0.5% SY-201 Ophthalmic Solution and the dosing schedule were chosen based on previous clinical studies, as described in Section 1.3.2.

3.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Procedures and Assessments (Appendix 1). The end of the study is defined as completion of the last visit or procedure shown in the schedule in the study.

4. Study Population

The study population will consist of approximately 200 adult subjects with moderate to severe DED.

The study eye is defined as the eye meeting all inclusion criteria and no exclusion criteria, and with the highest tCFS scoring at randomization (Visit 2, Day 1). If both eyes meet the inclusion criteria and no exclusion criteria and have the same tCFS score, the right eye will be used as the SE.

4.1 Inclusion Criteria

Individuals will be eligible for study participation if they meet all of the following criteria:

1. Provide written informed consent prior to any study-related procedures.
2. Are 18 years of age or older.
3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study.
4. Have a BCVA in each eye, using corrective lenses if necessary, of +0.7 logarithm of the minimum angle of resolution (LogMAR) or better as assessed by the Early Treatment of Diabetic Retinopathy Study (ETDRS) at Visit 1.
5. If women of childbearing potential (WOCBP), are non-lactating and have been sexually inactive (abstinent) for 14 days prior to Visit 1 and remain so through 30 days following Visit 6 or the last administration of the study drug or until completion of the subject's first menstrual cycle following the last administration of the study drug, whichever period of time is longer. Or they must have been using one of the following acceptable methods of birth control for the times specified:
    a. Intra-uterine device (IUD) in place for at least 3 months prior to Visit 1 through 30 days following Visit 6 or last administration of study drug or until completion of the subject's first menstrual cycle following last administration of the study drug, whichever period of time is longer.
    b. Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to Visit 1 through 30 days following Visit 6 or last administration of the study drug or until completion of the subject's first menstrual cycle following last administration of the study drug, whichever period of time is longer.
    c. Stable hormonal contraceptive for at least 3 months prior to Visit 1 through 30 days following Visit 6 or last administration of the study drug or until completion of the subject's first menstrual cycle following administration of the study drug, whichever period of time is longer. Note: For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following

administration of the study drug is not applicable, as females receiving this form of contraception will not have menses.

d. Surgical sterilization (vasectomy) of partner at least 6 months prior to Visit 1.

6. If postmenopausal women, have had no menstrual cycle for at least 1 year prior to Visit 1 or have undergone one of the following sterilization procedures at least 6 months prior to Visit 1:
   a. Bilateral tubal ligation
   b. Hysterectomy
   c. Bilateral oophorectomy
7. Have a history of DED in both eyes supported by a previous clinical diagnosis or have a history of subjective complaints for at least 6 months prior to Visit 1.

[redacted]

11. Are willing to withhold AT for the duration of the study, with the exception of rescue use of the study-provided AT (Refresh Plus®).

4.2 Exclusion Criteria

Individuals will be excluded from study participation if they meet any of the following criteria:

2. Any concomitant treatment or prior ocular procedure or surgery in either eye or alteration of the dose of systemic medications at the time of entry into the study that could interfere in the assessment of the trial, per the Investigator's judgment or per details below:
   a. Prior history of Isotretinoin (Accutane)
   b. Corneal refractive surgery, glaucoma surgery, or corneal transplantation within 2 years prior to Visit 1
   c. Altered use of nutraceuticals or multivitamins throughout the study
   d. Topical ophthalmic medications, including ocular hypotensive (glaucoma) medications, eye drops, gels, or AT (other than study-provided Refresh Plus®) throughout the study

   f. Penetrating intraocular surgery within 12 months prior to Visit 1
   g. Eyelid surgery or ocular surface surgery within 6 months prior to Visit 1
   h. Altered dose of the following used on a chronic basis within 3 months prior to Visit 1:
      - Anticholinergics

- Antidepressants
- Antihistamines
- Systemic immunosuppressive agents
- Oral steroids (dose must be <11 mg prednisone or equivalent/day)

  Dose must remain stable throughout study.

i. In either eye, have had punctal occlusion (cauterization or plugs [silicone or dissolvable]) within 3 months prior to Visit 1 or anticipate new or additional punctal occlusion during the duration of the study.

   NOTE: Permanent plugs lost should be replaced.

j. Any other Investigational Product within 45 days prior to Visit 1

k. Prescription treatments for ocular surface disease within 30 days prior to Visit 1, including

- Topical cyclosporine (Restasis®, Cequa®)
- Topical lifitegrast (Xiidra®)
- Ocular corticosteroids, including but not limited to fluorometholone and loteprednol etabonate (Eysuvis®)
- Varenicline (Tyvara®)

l. Autologous serum within 30 days prior to Visit 1

m. Altered dose of tetracycline compounds (tetracycline, doxycycline, or minocycline) within 30 days prior to Visit 1.

   Dose must remain stable throughout study.

n. Topical ocular antibiotics, topical ocular antihistamines or mast cell stabilizers, topical or nasal vasoconstrictors within 14 days prior to Visit 1

3. Have corneal erosive disease (e.g., confluent staining [NEI grade 4], confluent filaments) or other conditions suggestive of extensive damage of the cornea in either eye.
4. Have a history of glaucoma or IOP >25 mmHg at Visit 1 or a history of elevated IOP (>25 mmHg) in either eye.
5. Wear contact lenses for 14 days prior to Visit 1 or throughout the study.

[redacted]

7. Are considered legally blind in either eye (LogMAR BCVA ≥1.0 or Snellen BCVA ≤20/200).

[redacted]

9. Have a history of stem cell or bone marrow transplant.

[redacted]

g. Significant conjunctival scarring
h. Chemical burn
i. History of herpetic or neurotrophic keratitis
j. Serious systemic disease or uncontrolled medical condition that, in the judgment of the Investigator, could confound study assessments or limit compliance.

11. Have a history of liver, renal or hematological disease that, in the judgment of the Investigator, could confound the study assessments or impact subject safety.
12. Have an allergy to any component of the study drug formulation.
13. Have a documented history of ocular allergies in either eye that, in the judgment of the Investigator, are likely to have an acute increase in severity due to the expected timing of the exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.
14. Have systemic signs of infection (e.g., fever or current treatment with antibiotics).
15. Are an employee of a site that is directly involved in the management, administration, or support of this study or an immediate family member (grandparent, parent, sibling, child) of the same.
16. Have a known history of alcohol and/or drug abuse.
17. Are an active (daily) user of tobacco or marijuana.

19. Are unwilling or unable to comply with the study protocol.

4.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. Minimal information, including demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) will be recorded.

Individuals who do not meet the criteria for participation in this trial (screen failure) at the completion of Visit 1 because of the following may be rescreened:

- Prohibited medications from which the subject may discontinue for purposes of screening eligibility (with approval from Investigator based on clinical safety).
- Exclusionary medical history status at time of screening that will change (e.g., ocular infection, surgical history duration, etc.).

Rescreened subjects will be assigned a new participant number.

5. Study Treatments or Interventions

5.1 Investigational Products

Four (4) IPs will be administered during this study:

- SY-201 Ophthalmic Solution 2.0%
- SY-201 Ophthalmic Solution 1.0%
- SY-201 Ophthalmic Solution 0.5%
- Vehicle solution

5.1.1 Description

Table 1: Active and Vehicle IPs

	Active Investigational Product	**Vehicle Control (Placebo)**
Product	SY-201 Ophthalmic Solution	SY-201 Placebo
Dosage form	Solution/Drops	Solution/Drops
Unit dose	[redacted] (2.0% weight by volume [w/v]) [redacted] (1.0% w/v) (0.5% w/v)	[redacted] (0.0% w/v)
Route of administration	Topical ocular administration	Topical ocular administration
Ph sical descri tion	Sterile, colorless, clear li uid	Sterile, colorless, clear li uid

[redacted]

5.1.2 Dosage and Administration

This study includes a run-in period in which 1 drop of single-masked vehicle will be administered OU BID over 14 days. Administration of the double-masked IP, also 1 drop OU BID, will occur over a 60-day treatment period. In both periods, administration is preferred in the morning and evening, with 8 to 12 hours between instillations.

At Visit 1 (Day -14), subjects will be assigned of single-masked run-in roduct vehicle and self-administer their first dose under the supervision of the site staff.

Subjects will be instructed to instill the run-in product as 1 drop into each eye. Subjects will then take home their 3 assigned kits (sufficient for up to 15 days) of run-in product for self-administration. Subjects will dose at home that evening.

The used and unused containing single-masked run-in must be returned to the site at Visit 2 (Day 1). Subjects should **not** dose run-in product the day of Visit 2.

At Visit 2, randomized subjects will be assigned 2 IP kits of double-masked IP (SY-201 Ophthalmic Solution 2.0%, 1.0%, or 0.5% or vehicle). The first dose of double-masked IP, taken from an assigned kit, will be self-administered in the clinic by the subject under the supervision of the site staff. Subjects will be instructed to instill the IP as 1 drop into each eye. Subjects will be queried on drop comfort and then take home their 2 assigned kits (sufficient for up to 10 days) of double-masked IP for self-administration. Subjects will dose at home that evening.

Subjects will return the used and unused double-masked IP at each subsequent visit (through Visit 6) and receive new kits of double-masked IP to take home at Visit 3 (2 kits, sufficient for up to 10 days), Visit 4 (4 kits, sufficient for up to 20 days), and Visit 5 (7 kits, sufficient for up to 35 days).

5.2 Preparation/Storage/Handling/Accountability

5.2.1 Acquisition and Accountability

. The IP may be distributed by trained study staff. Used and unused IP will be maintained at the site for accountability by the clinical study monitor. When authorized by the Sponsor and after the clinical study monitor has verified drug accountability is complete and accurate, all used and unused single-masked (run-in) and double-masked IP will be returned for destruction.

5.2.2 Product Formulation, Appearance, Packaging and Labeling

[redacted]

Pouch labels will contain the following information: protocol number, contents, batch and pouch numbers, dosing instructions, storage temperature, Sponsor, and required statement(s) per regulatory agency.

Kit labels will contain the following information: protocol number, contents, batch and kit numbers, storage temperature, Sponsor, and required statement(s) per regulatory agency.

5.2.3 Product Storage and Stability

At clinical sites, IP will be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide IP to any subject not participating in this study. Subjects will be instructed on the proper storage of IP.

IP should be protected from light and stored inside the

5.2.4 Preparation

Neither SY-201 Ophthalmic Solution nor vehicle will require on-site preparation by the Investigator.

5.3 Measures to Minimize Bias: Randomization and Masking

To minimize bias, the treatment phase of this study is randomized and double-masked.

Subjects will be randomized to treatment assignment. If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data.

A randomization schedule will be generated by the electronic data capture (EDC) system. The EDC will be used for randomization and unmasking.

Double-masked IP—SY-201 (2.0%, 1.0%, or 0.5%) or vehicle—assigned to subjects at randomization will be identical in appearance. Sponsor, subjects, and investigative staff will be masked to the identity of treatment until completion of the study and final database lock.

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor after consultation with the Sponsor.

5.4 Treatment Compliance

Subjects are required to return all unused and used run-in product, IP, and study-provided AT. The materials returned will provide evidence of compliance.

5.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the electronic case report form (eCRF) are concomitant prescription medications, over-the-counter medications, and supplements.

All medications that the subject has taken 45 days prior to Visit 1 and through Visit 6 or discontinuation from the study will be recorded in the eCRF and the subject chart. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an AE will be recorded for each medication. Prior and concomitant medications (CMs) will be coded using the World Health Organization Drug Dictionary (WHODrug).

5.5.1 Prohibited Medications and Procedures

Prohibited medications and procedures that require a washout are also restricted throughout the study, unless otherwise noted.

Medication and Procedures Not Permitted	Minimum Washout Prior to Visit 1 (Unless Otherwise Noted)
Isotretinoin (Accutane)	Prior history
Corneal refractive surgery, glaucoma surgery, or corneal transplantation	2 years
Altered use of nutraceuticals or multivitamins	Throughout study
Topical ophthalmic medications, including ocular hypotensive (glaucoma) medications, eye drops, gels, or AT (other than study-provided Refresh Plus®)	Throughout study
[redacted]	Throughout study

Penetrating intraocular surgery	12 months
Eyelid surgery or ocular surface surgery	6 months
[redacted]	3 months
In either eye, have had punctal occlusion (cauterization or plugs [silicone or dissolvable]) or anticipate new or additional punctal occlusion during the duration of the study. NOTE: Permanent plugs lost should be replaced.	3 months
Any other IP	45 days
Prescription treatments for ocular surface disease, including • Topical cyclosporine (Restasis®, Cequa®) • Topical lifitegrast (Xiidra®) • Ocular corticosteroids, including but not limited to fluorometholone and loteprednol etabonate (Eysuvis®) • Varenicline (Tyvara®)	30 days
Autologous serum	30 days
Altered dose of tetracycline compounds (tetracycline, doxycycline, or minocycline). Dose must remain stable throughout study.	30 days
Contact lenses	14 days
Topical ocular antibiotics Topical ocular antihistamines or mast cell stabilizers Topical or nasal vasoconstrictors	14 days
[redacted]	

5.5.2 Artificial Tears

AT, whether subject- or study-supplied, is prohibited during the run-in period of the study (Visit 1 to Visit 2). Any subject who violates this policy will not be randomized to treatment and will be discontinued from the study.

Preservative-free AT (Refresh Plus®) will be provided for rescue use during the treatment phase of the study (Visits 2 through 6) but limited to ≤2 instillations per day. Subjects will be required to record AT use in a diary and return the used and unused AT at clinic Visits 2 through 6; subjects will be queried about AT use at each clinic visit.

6. Study Discontinuation/Participant Withdrawal

6.1 Discontinuation of Study Treatment or Intervention

The study IP may be discontinued by a subject at any time, although every effort will be made to ensure consistent subject participation over the 60-day treatment period. In the event of discontinuation of IP by a subject, the Investigator will make every attempt to have the subject complete Visit 6 assessments as soon as possible. The subject will be discontinued following those assessments, and the reason for premature discontinuation will be recorded in the subject chart and entered in the eCRF.

6.2 Participant Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a subject from the study for the following reasons:

- Withdrawal of consent
- Study terminated by the Sponsor
- Lost to follow-up
- Pregnancy
- Significant study treatment/intervention non-compliance
- If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Disease progression that requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for subject discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study intervention may be replaced.

Those who sign the ICF, are randomized, receive the study treatment/intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

In the event of study discontinuation, the Investigator will make every attempt to have the subject complete Visit 6 assessments as soon as possible. The reason for premature discontinuation will be recorded in the subject chart and entered in the eCRF.

6.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return for a required clinic study visit:

- The site will attempt to contact the subject and reschedule the missed visit within 1 week, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will be documented in the subject's medical record or study file.

Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7. Study Procedures

Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all subjects prior to any study-related procedures being performed. The Schedule of Procedures and Assessments (Appendix 1) lists the procedures that should occur at each study visit.

7.1 Visit Descriptions

7.1.1 Screening (Visit 1, -14 days)

Ocular assessments and procedures must be performed in the order specified below. Tasks marked with an asterisk may be performed at any point (at Visit 1, after the consent is signed).

- Explain the purpose and conduct of the study to the subject, answer the subject's questions, and obtain written informed consent and HIPAA authorization.
- Assign Subject Identification Number.
- Obtain information including: demographics, CMs, ocular and systemic medical and medication history and surgical history.
- Determine study eligibility based on Inclusion/Exclusion criteria.
- Administer the following subject-rated symptom assessments:

- Urine pregnancy test (UPT) for WOCBP*
- Safety labs: blood samples for chemistry and hematology*
- BCVA
- [redacted]
- Biomicroscopy and external eye exam
- OU tear collection under slit lamp for biomarker test (quantitative point-of-care [POC] MMP-9 test by Seinda Biomedical Corp.)
- CFS
  - **Note:** After CFS grading, wait at least 15 minutes before conducting
-
- IOP
- Dilated ophthalmoscopy
- Enter subject information into EDC to determine the single-masked run-in kit number.
- Dispense 3 kits of single-masked run-in product (sufficient for up to 15 days) and explain the method of run-in administration.

- Observe as the subject self-administers the first dose (1 drop OU) of single-masked run-in at the clinic. All remaining doses (1 drop OU BID) will be administered by the subject at home.
- Assess for AEs.
- Remind subject:
    - Use of AT during the run-in period is prohibited. Use will result in subject's discontinuation from the study.
    - Run-in product should be administered as 1 drop OU once in the morning and once in the evening, 8-12 hours apart. **Do not dose run-in product the day of Visit 2.**
    - Return all used and unused run-in product at Visit 2.

7.1.2 Randomization (Visit 2, Day 1)

The following procedures will be performed at Visit 2:

- Confirm study eligibility based on Inclusion/Exclusion criteria.
- Update CMs
- Assess AEs
- Administer the following subject-rated symptom assessments:

- BCVA
-
- Biomicroscopy and external eye exam
- OU tear collection under slit lamp for biomarker test (quantitative POC MMP-9)
- CFS
    - **Note:** After CFS grading, wait at least 15 minutes before conducting
-
- IOP
- Confirm that the subject is eligible for randomization. The trained site staff will then conduct the following procedures:
    - Enter subject information into Interactive Web Randomization System (IWRS) to determine randomization code and kit number.
    - Explain the method of IP administration. Evaluate the subject's instillation technique.
    - Dispense 2 double-masked IP kits (sufficient for up to 10 days) to the subject to take home.
    - Observe as the subject self-administers the first dose of double-masked IP at the clinic/site. All remaining doses will be administered by the subject at home, OU BID (morning and evening, instillations approximately 8-12 hours apart).

- Drop comfort assessment
- Issue AT diary and train subject in diary completion.
- Dispense preservative-free AT (Refresh Plus®) and counsel subject to limit AT use to ≤2 instillations per day.

7.1.3 Visit 3 (Day 7 ± 2 days)

The following procedures will be performed at Visit 3:

- Update CMs
- Assess AEs
- Administer the following subject-rated symptom assessments:

- BCVA
-
- Biomicroscopy and external eye exam
- SE tear collection under slit lamp for biomarker test (quantitative POC MMP-9)
- CFS
- IOP
- Collect AT diary and all used and unused AT and IP.
- Issue new AT diary.
- Dispense preservative-free AT (Refresh Plus®) and remind subject to limit AT use to ≤2 instillations per day.
- Dispense 2 double-masked IP kits (sufficient for up to 10 days) to the subject to take home.

7.1.4 Visit 4 (Day 14 ± 2 days)

The following procedures will be performed at Visit 4:

- Update CMs
- Assess AEs
- Administer the following subject-rated symptom assessments:

- BCVA
-
- Biomicroscopy and external eye exam
- SE tear collection under slit lamp for biomarker test (quantitative POC MMP-9)
- CFS

- IOP
- Collect AT diary and all used and unused AT and IP.
- Issue new AT diary.
- Dispense preservative-free AT (Refresh Plus®) and remind subject to limit AT use to ≤2 instillations per day.
- Dispense 4 double-masked IP kits (sufficient for up to 20 days) to the subject to take home.

7.1.5 Visit 5 (Day 28 ± 2 days)

The following procedures are to be performed at Visit 5:

- Update CMs
- Assess AEs
- Administer the following subject-rated symptom assessments:

- BCVA
-
- Biomicroscopy and external eye exam
- SE tear collection under slit lamp for biomarker test (quantitative POC MMP-9)
- CFS
- IOP
- Collect AT diary and all used and unused AT and IP.
- Issue new AT diary.
- Dispense preservative-free AT (Refresh Plus®) and remind subject to limit AT use to ≤2 instillations per day.
- Dispense 7 double-masked IP kits (sufficient for up to 35 days) to the subject to take home.
- Dosing and drop comfort assessment will take place **in clinic** at Visit 6. Advise subject to withhold 1 dose of IP on the day of Visit 6.

7.1.6 Visit 6 (End of Study/Early Termination, Day 60 ± 3 days)

The following procedures are to be performed at the End of Study visit:

- Update CMs
- Assess AEs
- Administer the following subject-rated symptom assessments:

- UPT for WOCBP*

- Safety labs: blood samples for chemistry and hematology*
- BCVA
-
- Biomicroscopy and external eye exam
- SE tear collection under slit lamp for biomarker test (quantitative POC MMP-9)
- CFS
  - **Note:** After CFS grading, wait at least 15 minutes before conducting
-
- IOP
- Dilated ophthalmoscopy
- IP administration and drop comfort assessment
- Collect AT diary and all used and unused AT and IP.

7.1.7 Unscheduled Visits

At times outside of normally scheduled visits, assessments will be conducted at the discretion of the Investigator.

7.1.8 Early Termination

In the event that a subject exits or is terminated from the study prior to the End of Study visit (Visit 6), every attempt will be made to ensure that all Visit 6 assessments are performed prior to the subject being discharged.

8. Study Assessments

The Schedule of Procedures and Assessments (Appendix 1) provides a list of study assessments and evaluations to be performed and the timing of each.

8.1 Efficacy Evaluations

Efficacy assessments will be conducted at the time points indicated on the Schedule of Procedures and Assessments (Appendix 1).

- tCFS (mNEI scale, 0-20) (Appendix 3)

8.2 Safety Evaluations

Safety assessments will be performed at the time points indicated on the Schedule of Procedures and Assessments (Appendix 1).

- AE monitoring (Section 8.2.1)
- Safety labs (chemistry and hematology) (Section 8.2.2)
- BCVA (Appendix 9)
- Slit lamp biomicroscopy and external eye exam (Appendix 10)
- IOP (Appendix 11)
- Dilated ophthalmoscopy (Appendix 12)
- Drop comfort assessment (Appendix 13)

8.2.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Adverse events will be monitored throughout the study. Subjects will be encouraged to report any adverse findings during the study whether or not they are related to IP. These can be collected either in an unsolicited fashion without any prompting or in response to a general question such as: “Have you noticed anything different since you started the study; began the IP, etc.?”

All AEs will be captured on the appropriate case report form (CRF). Information to be collected at minimum includes event description, onset, assessment of severity, relationship to IP, and outcome.

The Investigator will record all AEs with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the subject is screened will be considered baseline and not reported as an AE. However, if the subject's condition deteriorates at any time during the study, it will be recorded as an AE.

8.2.1.1 Definitions

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

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

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

8.2.1.2 Classification of Adverse Events

Severity of Adverse Events

The severity of all AEs will be assessed by the Investigator and graded as follows:

- **Mild:** requires minimal or no treatment and do not interfere with the subject's daily activities
- **Moderate:** results in a low level of inconvenience or concern and may cause some interference with functioning

- **Severe:** interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. The term "severe" does not necessarily equate to "serious."

Relationship of Adverse Events

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the IP must always be suspect.

- **Unrelated:** no reasonable possibility that the administration of the IP caused the event, no temporal relationship between the IP and event onset, or an alternate etiology has been established
- **Related:** is known to occur with the IP, is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB), package insert, or device labeling or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a *class of drugs* (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the IP, but are not specifically mentioned as occurring with the particular IP under investigation.

The Investigator will be responsible for determining whether an AE is unexpected, i.e., if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP.

8.2.1.3 Adverse Event Reporting Requirements

According to federal regulations, an Investigator must immediately report (within 24 hours) to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or IB, and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor (See 21 Code of Federal Regulations [CFR] 312.64(b)).

According to federal regulations, the Sponsor must notify the US Food and Drug Administration (FDA) and all participating Investigators as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that a potential serious risk arising from a clinical study qualifies for reporting. The Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event (See 21 CFR 312.32(c)(1)).

Furthermore, the Sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information (See 21 CFR 312.32(c)(2)).

8.2.1.4 Other Events of Interest

Not applicable.

8.2.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed through Visit 6.

Any report of pregnancy for any female study subject must be reported within 24 hours to the Sponsor's Safety Department or its delegate using the Pregnancy Report Form. The pregnant female subject must be withdrawn from the study.

Every effort will be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days after delivery.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sponsor's Safety Department using the Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to the Sponsor's Safety Department.

8.2.2 Clinical Laboratory Tests

The following clinical laboratory tests will be performed at the time points indicated on the Schedule of Procedures and Assessments (Appendix 1) and as detailed below and in the laboratory reference manual.

- Chemistry

  - Sodium, Potassium, BUN, Creatinine, Glucose, Calcium, Phosphorus, Total Protein, Albumin, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Chloride, Bicarbonate

- Hematology
  - Hemoglobin, Hematocrit, RBC, MCH, MCHC, RDW, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Platelets

9. Statistical Considerations

Continuous measures will be summarized descriptively by the mean, standard deviation, median, minimum, and maximum values. Categorical measures will be summarized by the frequency and percentage of subjects.

A separate Statistical Analysis Plan (SAP) will be prepared prior to unmasking of study data.

9.1 Statistical Hypothesis

It is hypothesized that SY-201 Ophthalmic Solution will be safe and improve DED signs and symptoms in subjects with a documented diagnosis of DED. In particular, efficacy will be assessed using the following endpoints at Day 60:

- Mean CFB in tCFS (mNEI scale)
- [redacted]

To control for type I error, comparisons will be made within each active dose level of SY-201 Ophthalmic Solution compared to vehicle. In other words, the primary endpoints will be compared sequentially between SY-201 Ophthalmic Solution 2.0% and vehicle, first testing tCFS and, if statistically significant, then Should both endpoints achieve statistical significance for the 2.0% dose, testing will proceed to SY-201 O hthalmic Solution 1.0% versus vehicle, first testing tCFS and, if statistically significant, then . Should both endpoints achieve statistical significance for the 1.0% dose, testing will proceed to SY-201 Ophthalmic Solution 0.5% and vehicle, first testing tCFS and, if statistically significant, then In other words, the first non-significant result in this testing hierarchy of six hypotheses will imply that subsequent tests are non-significant.

9.2 Sample Size Determination

For mean change from baseline to Day 60 in tCFS, a sample size of 45 SY-201–treated subjects versus 45 vehicle-treated subjects will have 87.9% power to detect an effect size of 2.0 units with a standard deviation of 3.0 for an unpaired t-test with a 2-sided alpha = 0.05.

For mean change from baseline to Day 60 in dry eye symptom , a sample size of 45 SY-201–treated subjects versus 45 vehicle-treated subjects will have 83.5% power to detect an effect size of 1.5 units with a standard deviation of 2.4 for an unpaired t-test with a 2-sided alpha = 0.05.

Fifty (50) subjects per treatment arm, for a total 200 subjects, will be enrolled to allow for some dropout of subjects.

9.3 Analysis Populations

The Full Analysis Set (FAS) consists of all subjects Subjects will be analyzed in the group to which This set will be used for the analysis of all efficacy endpoints as the primary analysis.

The Per Protocol (PP) Analysis Set will include all subjects who completed study-required treatment and who followed the protocol without significant deviations. The determination of significant protocol violations will be made prior to locking the final database and unmasking. Subjects will be analyzed in the group according to the treatment received.

The Safety Analysis Set will include all subjects who took at least one dose of investigational product as indicated on the dosing record. Subjects will be analyzed in the group according to the treatment received. All safety variables will be analyzed using the Safety Analysis Set and only observed data will be included (i.e., missing data will remain missing for the safety analysis).

9.4 Statistical Analyses

The statistical analysis of the study will be performed on the data through Day 60, after all subjects have either completed the Day 60 visit or discontinued early from the study and after the study database has been cleaned, verified, and locked. It is planned that the data from all clinical sites that participate in this study will be combined so that the target sample size will be available for analysis.

Analyses will be conducted on individual SY-201 arms versus vehicle arm.

9.4.1 Baseline Descriptive Analyses

Demographic characteristics including age (years), sex, race, and ethnicity will be summarized by treatment group and overall. Medical history [coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA)], and prior and concomitant medications (coded using the most recent version of the WHODrug) will be summarized by treatment and overall.

The numbers of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, poor compliance, rescue due to lack of efficacy). A list of discontinued subjects, protocol deviations, and subjects excluded from the analysis sets will be provided as well.

Exposure and compliance to study treatment will be summarized by treatment and overall.

9.4.2 Efficacy Analyses

In general, efficacy analyses will be performed using the FAS and the observed data at each visit for the study eye and qualifying non-study eyes for most ocular measures or overall for subject-level measurements. In the case of the biomarker test (MMP-9), analysis will be for the study eye only. Analysis of mean CFB in tCFS and eye [redacted] will also be performed using the PP Analysis Set as documented in the SAP.

9.4.2.1 Primary Efficacy Analyses

Primary Estimands: The primary estimands are the treatment differences between SY-201 Ophthalmic Solution arms and vehicle for mean CFB to Day 60 in tCFS using study eyes and mean CFB to Day 60 in [redacted] score using the FAS.

Target Population: Subjects with DED who meet the study entry criteria.

Treatment Condition(s): Treatment condition is based on the randomized treatment group.

Population-level Summaries: The difference in the mean CFB to Day 60 in tCFS using study eyes and the difference in mean CFB to Day 60 in [redacted] score and their p-values and corresponding 95% confidence intervals.

The proposed procedures to handle missing data and intercurrent events are as follows:

- Discontinuation of study therapy with continued participation in the study
  - Treatment Policy – no imputation; use observed data
- Receipt of rescue therapy
  - Treatment Policy – no imputation; use observed data
- Missing data with or without withdrawal, regardless of reason
  - Hypothetical approach – missing data will be accounted for assuming missing at random (MAR) using mixed-model repeated measures (MMRM).

Mean CFB in tCFS will be analyzed using an MMRM model. The model will include the baseline measurement, treatment, time, and treatment by time interaction as fixed effects, with a random effect for site. An unstructured covariance among repeated measurements is assumed. A similar model for the subject-level mean CFB in [redacted] score will be used.

Additional sensitivity analyses will be described in the SAP.

9.4.2.2 Secondary Efficacy Analyses

[redacted]

9.4.3 Safety Analyses

Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular AEs, laboratory measurements, BCVA, IOP, ophthalmic exams using slit lamp biomicroscopy and dilated ophthalmoscopy, and drop comfort assessment. Summaries will be provided by treatment group, and for ocular assessments separately by eye.

9.4.3.1 Adverse Events

AEs will be coded using MedDRA (most current version) and categorized by system organ class using preferred terms. Separate summaries of AEs related to treatment (as reported by the Investigator) and by severity will be presented. The number of deaths and SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

9.4.3.2 Clinical Laboratory Tests

Summary statistics for observed and CFB for serum chemistry and hematology laboratory tests will be presented.

9.4.3.3 Other Safety Evaluations

Summary statistics for observed and CFB for BCVA, IOP, and drop comfort assessment will be presented. Abnormalities in slit lamp biomicroscopy and dilated ophthalmoscopy will be summarized by frequency and percentage.

9.5 Interim Analysis

Not applicable.

9.6 Subgroup Analyses

Subgroup analyses will include testing of the mean CFB in tCFS, [redacted] score, and secondary endpoints in subgroups based on MMP-9 level in the [redacted] at baseline (Visit 2): subjects with elevated MMP-9 level and The threshold for elevated MMP-9 will be defined in the SAP.

Additional subgroup analyses will be described in the SAP.

9.7 Exploratory Analyses

Not applicable.

9.8 Missing or Unused Data

Missing data for primary endpoints will be considered MAR with the analysis using MMRM. Otherwise, observed data will be analyzed. All data collected in this study will be presented in individual subject data listings for all subjects at each visit.

9.9 Tabulation of Individual Participant Data

All data collected in this study will be presented in individual subject data listings for all subjects.

10. Supporting Documentation and Operational Considerations

10.1 Regulatory Issues, Ethical Concerns, and Study Oversight

10.1.1 Informed Consent Process

10.1.1.1 Consent Documents

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to any procedures being done specifically for the study.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB) approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. The participant will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant should have the opportunity to discuss the study with his/her family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed and dated informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigators, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) Sponsor, and regulatory authorities as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and the Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension may include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and/or FDA.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality will be extended to cover testing of laboratory samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The Study Monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product will be able to inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (i.e., office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Lexitas Pharma Services, Inc. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Lexitas Pharma Services, Inc., research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Lexitas Pharma Services, Inc.

10.1.4 Clinical Monitoring

Lexitas Pharma Services, Inc., will conduct the clinical monitoring for this study. A Clinical Monitoring Plan (CMP) is to be used, which will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.5 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practice [GMP]).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.1.6 Data Handling and Record Keeping

10.1.6.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, CMs, and expected adverse reactions data) and clinical laboratory data will be entered into IBM Clinical, a 21 CFR Part 11-compliant data capture system provided by Lexitas Pharma Services, Inc. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.6.2 Study Records Retention

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 25 years, to meet international registration requirements. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be on the part of the participant, the Investigator, or the study site staff. As a result of major deviations, corrective actions are to be developed by the site and implemented promptly. Details concerning minor, major, and critical protocol deviations will be outlined in a CMP or MOP.

It is the responsibility of the site's Investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to the IRB and Lexitas Pharma Services, Inc., and/or Sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.8 Publication and Data Sharing Policy

All information provided concerning the drug and clinical trial is confidential and belongs to the Sponsor. The Investigator may use this information only in relation to the trial. He/she will also be obliged to provide the Sponsor with all data generated in the study.

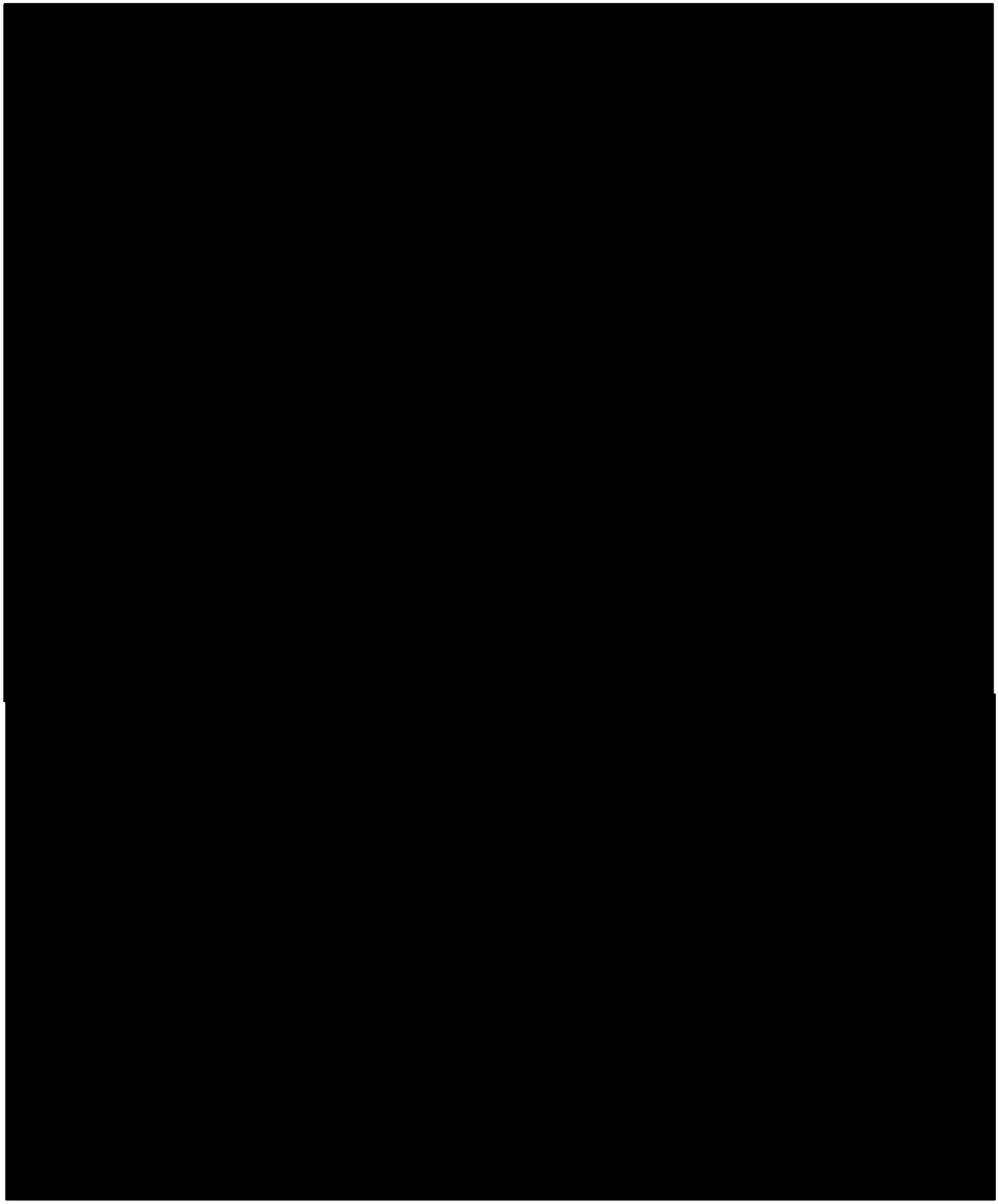
All results, data, and information developed, generated, and derived from this clinical trial, including any inventions, processes, or improvements that may arise from conducting the clinical trial, shall be the sole property of the Sponsor and, therefore, the Investigator agrees to treat this information as confidential and secret as mentioned above. The Investigator agrees not to disclose the information in any way without the prior written consent of the Sponsor.

The Sponsor and Investigators agree to the publication and wide dissemination of the results of this study. This study constitutes a joint effort between the Sponsor and the Investigators and, as such, both parties agree that either party can make recommendations on articles or texts which shall be considered in preparing final scientific documents for publication or presentation. All publications and presentations proposed by the Investigators or their staff and associates that are derived or are related to this study must be sent to the Sponsor for review 90 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable aspects that, at the discretion of the Sponsor alone, justify the protection of intellectual or industrial property, the Sponsor may delay any publication or presentation for a maximum of 90 days in order to request such protection.

In accordance with national and local regulations, this study protocol shall be presented in a clinical trial register for public access and shall receive a unique identification number. In addition, the results of this clinical study shall be revealed in an accessible clinical trial results database, regardless of the outcome.

11. References



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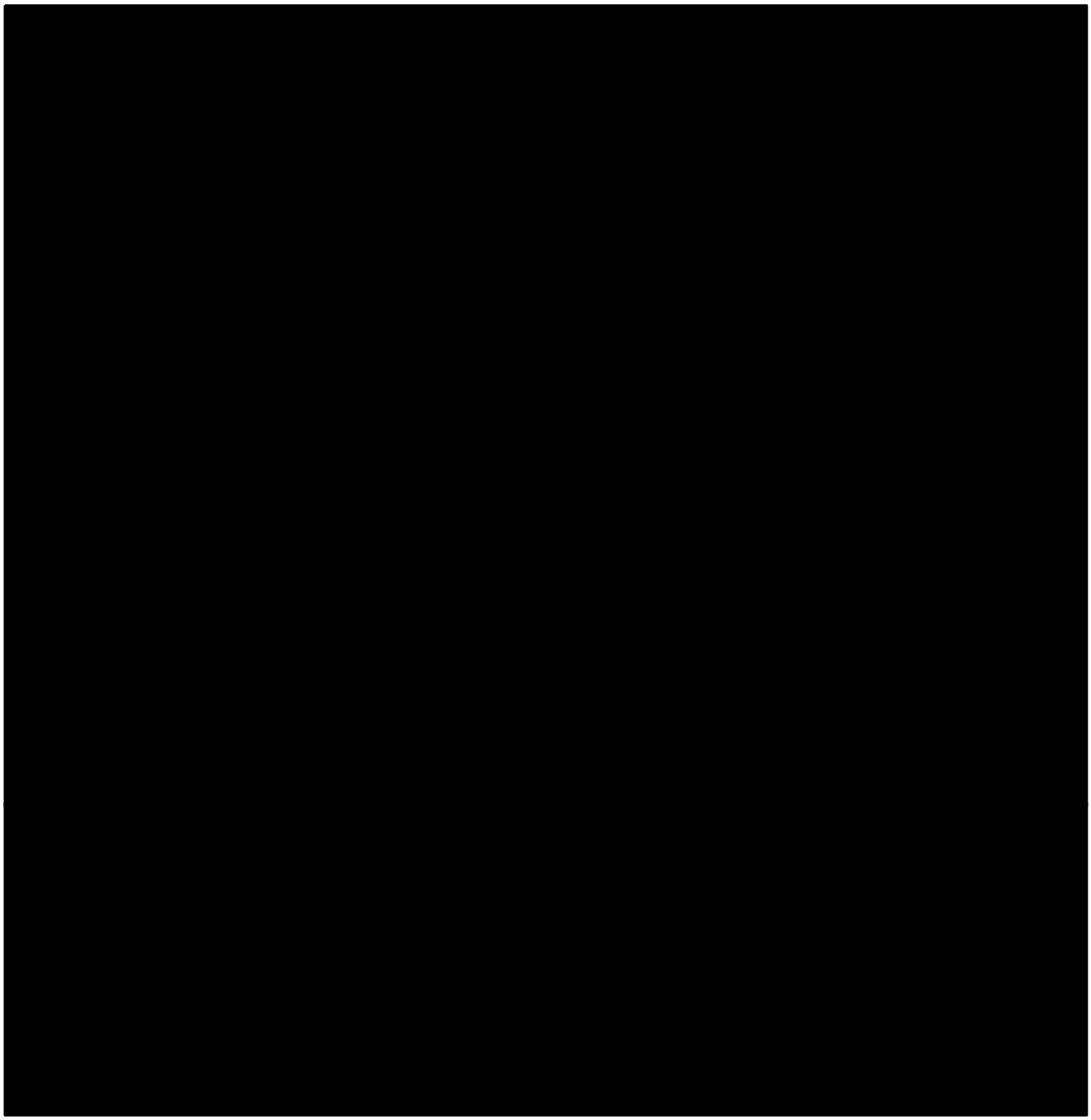


12. Appendices

12.1 Appendix 1: Schedule of Procedures and Assessments

Study Period	Screening	Treatment Period				End of Study/ET
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**
Study Day	**-14**	**1**	**7**	**14**	**28**	**60**
Informed consent	**X**					
Inclusion/exclusion criteria	**X**	**X**				
Demographics/medical history	**X**					
Concomitant medications query	**X**	**X**	**X**	**X**	**X**	**X**
AE query	**X**	**X**	**X**	**X**	**X**	**X**
[redacted]	**X**	**X**	**X**	**X**	**X**	**X**
[redacted]	**X**	**X**	**X**	**X**	**X**	**X**
UPT for WOCBP	**X**					**X**
Serum chemistry and hematology	**X**					**X**
BCVA	**X**	**X**	**X**	**X**	**X**	**X**
Biomicroscopy and external eye exam	**X**	**X**	**X**	**X**	**X**	**X**
[redacted]	**X**	**X**	**X**	**X**	**X**	**X**
Tear collection for biomarker test (POC MMP-9)[a]	**X**	**X**	**X**	**X**	**X**	**X**
CFS	**X**	**X**	**X**	**X**	**X**	**X**
[redacted]	**X**	**X**				**X**
IOP	**X**	**X**	**X**	**X**	**X**	**X**
Dilated ophthalmoscopy	**X**					**X**
In-clinic administration of run-in product or IP	**X**	**X**				**X**
Drop comfort assessment		**X**				**X**
Dispense run-in product or IP for home administration	**X**	**X**	**X**	**X**	**X**	
Dispense preservative-free AT		**X**	**X**	**X**	**X**	
Issue and/or collect AT diary		**X**	**X**	**X**	**X**	**X**
Collect used and unused run-in product, AT, and/or IP		**X**	**X**	**X**	**X**	**X**

[a]MMP-9 will be assessed OU at Visits 1 and 2 and SE thereafter.
[b]Wait at least 15 minutes after grading CFS before conducting

Abbreviations: AE = adverse event; AT = artificial tears; BCVA = best corrected visual acuity; CFS = corneal fluorescein staining; ET = early termination IOP = intraocular ressure IP = investi ational product; MMP-9 = matrix metalloproteinase-9; POC: point-of-care; SE = study eye; UPT = urine pregnancy test; WOCBP = women of childbearing potential

12.2 Appendix 2: Abbreviations and Definition of Terms

AE	Adverse event
[redacted]	
ALT (SGPT)	Alanine aminotransferase test, serum glutamic pyruvic transaminase
AST (SGOT)	Aspartate aminotransferase test, serum glutamic-oxaloacetic transaminase
AT	Artificial tears
BCVA	Best corrected visual acuity
BFS	Blow-fill-seal
BID	*Bis in die* (twice daily)
BUN	Blood urea nitrogen
[redacted]	
CFB	Change from baseline
CFR	Code of Federal Regulations
CFS	Corneal fluorescein staining
CMs	Concomitant medications
CMP	Clinical monitoring plan
CRF	Case report form
CS	Clinically significant
DED	Dry eye disease
DMFC	Disposable micro-capillary fluid collector
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination

ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
[redacted]	
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IL	Interleukin
IND	Investigational New Drug
IOP	Intraocular pressure
IP	Investigational product
IPL	Intense pulsed light
IRB	Institutional Review Board
IUD	Intra-uterine device
IWRS	Interactive Web Randomization System
[redacted]	
[redacted]	
LogMAR	Logarithm of the minimum angle of resolution
M1	Classically activated macrophages
M2	Alternatively activated macrophages

MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MMP-9	Matrix metalloproteinase-9
MMPs	Matrix metalloproteinases
MMRM	Mixed-model repeated measures
mNEI	Modified National Eye Institute (scale)
MOP	Manual of Procedures
NCS	Non-clinically significant
NEI	National Eye Institute
NIH	National Institutes of Health
OSDI	Ocular Surface Disease Index
OU	*Oculus uterque* (both eyes)
PI	Principal Investigator
POC	Point-of-care
PP	Per Protocol
PRN	*Pro re nata* (as needed)
QC	Quality control
RBC	Red blood cell count
RDW	Red cell distribution width
SAE	Serious adverse event
[redacted]	
SAP	Statistical Analysis Plan

SE	Study eye
SOP	Standard Operating Procedure
TBUT	Tear film break-up time
tCFS	Total corneal fluorescein staining
TNTC	Too numerous to count
Treg	Regulatory T cell
UPT	Urine pregnancy test
US	United States
VA	Visual acuity
[redacted]	
WBC	White blood cell count
WHODrug	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential
w/v	Weight by volume

12.3 Appendix 3: Corneal Fluorescein Staining (CFS), Modified NEI Scale

The Investigator should use sufficient unpreserved saline solution (study stock) to wet the entire area of fluorescein impregnation on a 1.0 mg strip. If the strip becomes too saturated, discard and begin again with a new strip. Within 15 seconds of wetting the strip, taking care not to touch the strip to the eye, instill the fluorescein sodium in the inferior cul-de-sac. Instruct the subject to blink several times to distribute the fluorescein staining.

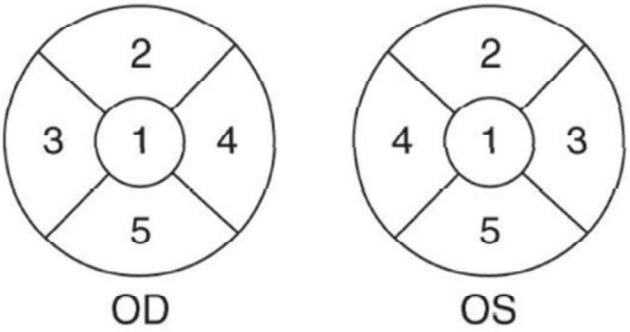
The Investigator should wait approximately 2 minutes after instillation of fluorescein before evaluating staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining.

The cornea is divided into 5 sectors (central, superior, inferior, nasal, and temporal), each of which is scored on a scale of 0–4 in increasing increments of 0.5. Grade each of the 5 sectors of the cornea (central, superior, inferior, nasal, and temporal) in each eye. Total score (0-20) is obtained by summing the 5 sections of the cornea.

The grading results for each area, as well as the total score obtained from the scoring of the cornea, are to be recorded in the eCRF. Whenever possible, the same Investigator should perform the grading per subject.

Section 1 = Central, 2 = Superior, 3= Temporal, 4 = Nasal, 5= Inferior

OD: *Oculus dexter* (right eye)
OS: *Oculus sinister* (left eye)



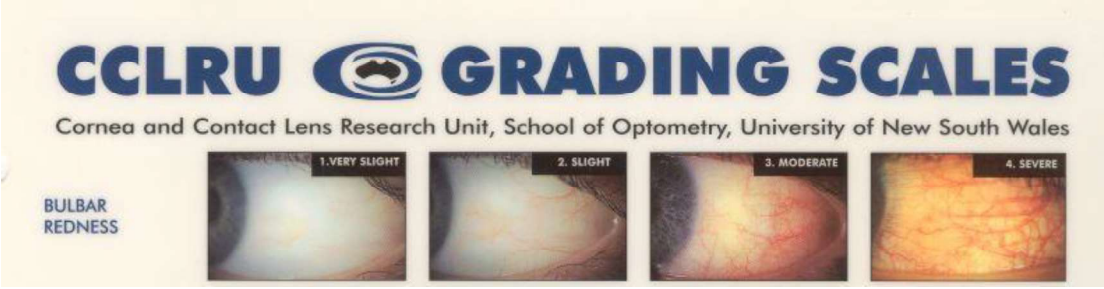
Grade	Punctate Stain Spots
0	0 spots
0.5	1-7 spots
1.0	8-15 spots
1.5	16-22 spots
2.0	23-30 spots
2.5	31-37 spots
3.0	≥38 spots or too numerous to count (TNTC), must be **<½ area**, may be confluent but **not coalescent**
3.5	≥38 spots or TNTC, must be **>½ area**, may be confluent but **not coalescent**
4.0	≥38 spots or TNTC, **must have coalescent area**

12.4 Appendix 4:

12.5 Appendix 5:

12.6 Appendix 6: Bulbar Conjunctival Hyperemia

Investigators will rate overall bulbar conjunctival hyperemia using the CCLRU grading scale. A score of 0 will be given if there is no bulbar redness.

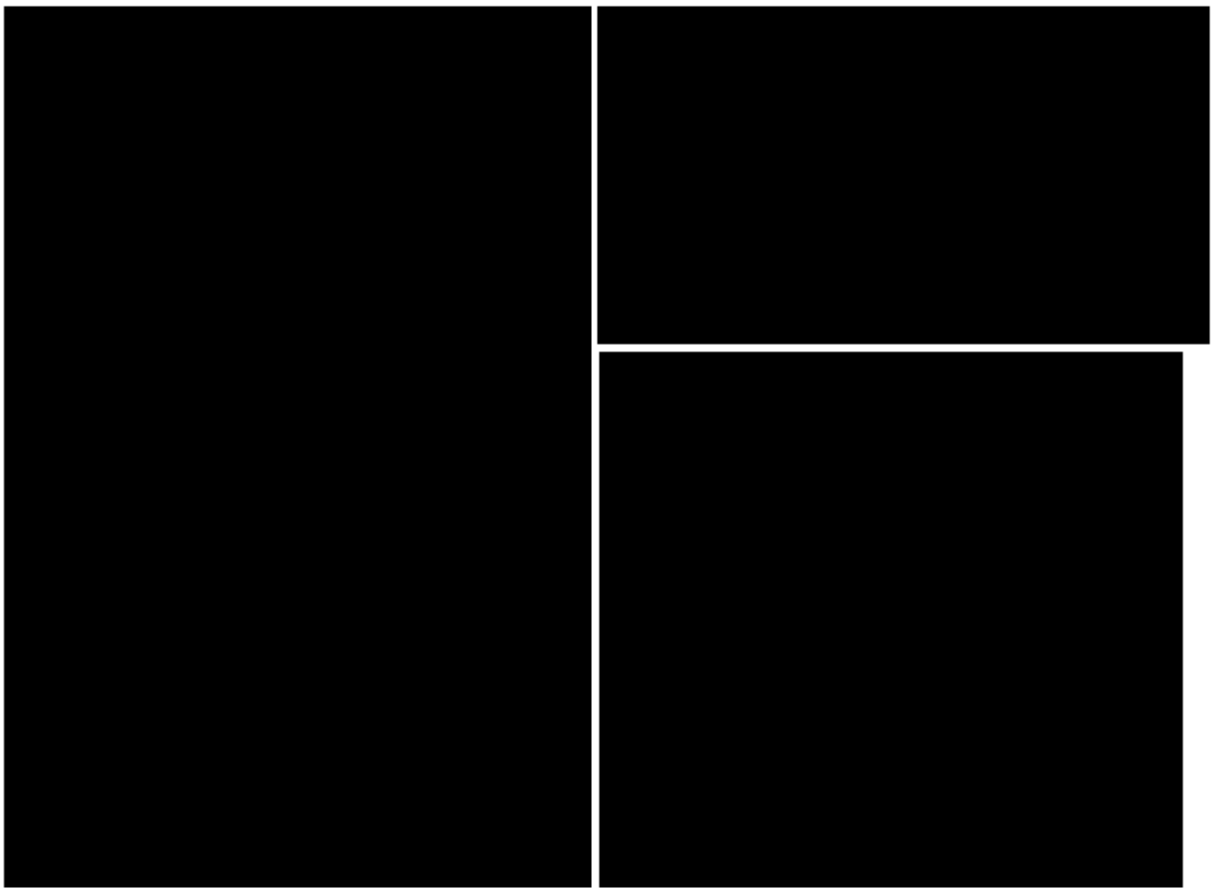


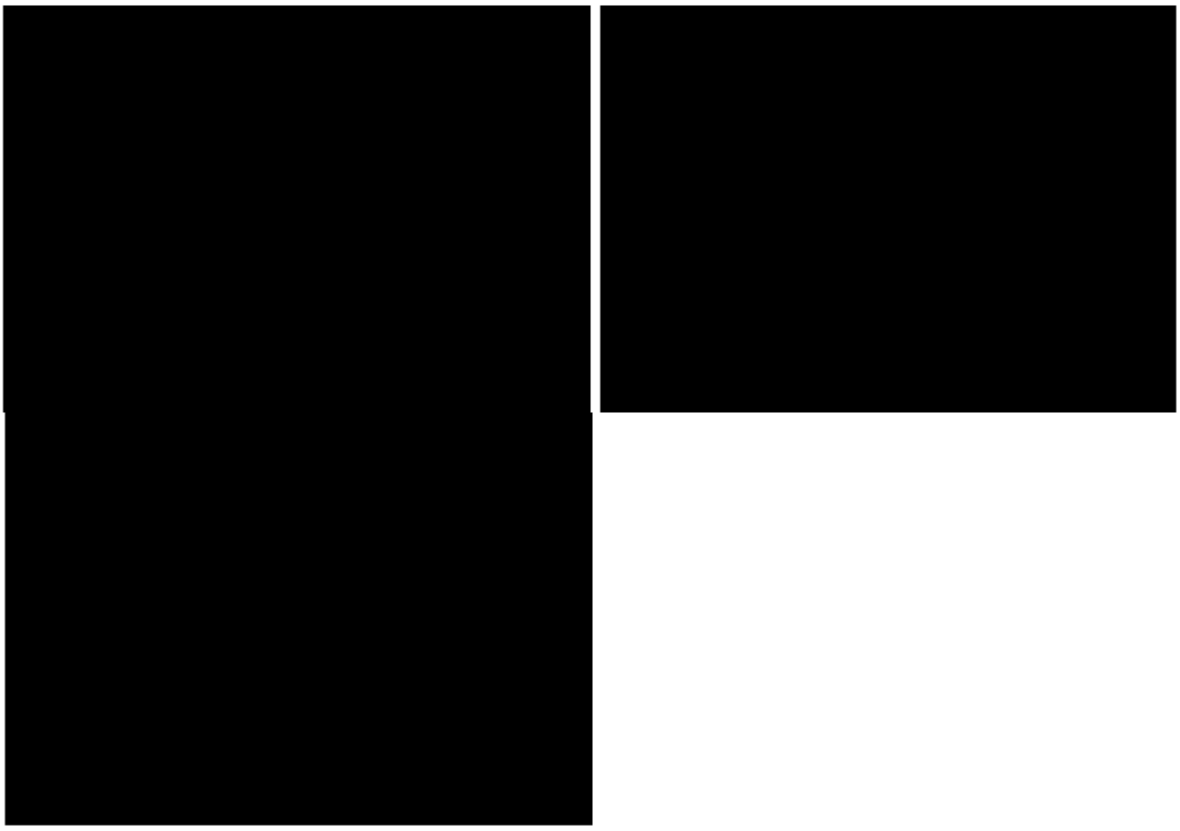
12.7 Appendix 7: Biomarker Test (MMP-9)

The MMP-9 point-of-care kit is manufactured by Seinda Biomedical Corp. (Guangzhou, China) and contains a disposable micro-capillary fluid collector (DMFC), MMP-9 test card, dropper bottle of reaction buffer, and i-ImmunDx™ Analyzer. MMP-9 is to be collected OU at Visits 1 and 2 and only SE thereafter.

Collect non-stimulated tear fluid from the outer corner of the eye at the lateral canthus using the DMFC, with a slit lamp.

When tear fluid fills the microcapillary tip of the DMFC, stop collecting and dispense tear fluid in the sample hole of the provided MMP-9 test card. Apply 3 drops of reaction buffer. Wait 15 minutes, then insert the test card into the i-ImmunDx™ Analyzer and obtain a quantitative result.





12.8 Appendix 8: Unanesthetized Schirmer Test

The Schirmer test will be conducted on unanesthetized eyes. A 35 mm x 5 mm filter paper strip is used to measure the amount of tears produced over 5 minutes. The strip is placed in the lower eyelid margin of both eyes. After 5 minutes, the strip is removed and the amount of wetting is measured in millimeters.

Unanesthetized Schirmer test must be performed at least 15 minutes after fluorescein application and evaluation of CFS.

12.9 Appendix 9: Best Corrected Visual Acuity (BCVA)

Visual acuity (VA) testing should precede any examination requiring contact with the eye or instillation of study dyes, as is detailed in the order of assessments for each visit in Section 7.1. LogMAR visual acuity must be assessed using an ETDRS or modified ETDRS chart. VA testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

An ETDRS or modified ETDRS chart may be used. If a Lighthouse chart is used (24.5" by 25"; either reflectance or retro-illuminated), the subject must view the chart from a distance of exactly 4 meters (13.1 feet). If smaller reproductions (18" by 18", e.g., Prevent Blindness) are used, the subject viewing distance should be exactly 10 feet. Reflectance wall charts should be frontally illuminated (60-watt bulb or a well-lit room).

The subject should be positioned according to the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The subject should be asked to read slowly, about 1 letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. If the subject changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart; the subject should be encouraged to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessments of visual acuity during the study, the same lighting conditions must be used consistently throughout the study

Calculations: LogMAR VA = Baseline value + (n X 0.02)

where: the baseline value is the LogMAR number of the last line read (at least 1 letter read correctly in this line), and "n" is the total number of letters missed up to and including the last line read, and "0.02" is the value for each letter.

12.10 Appendix 10: Slit Lamp Biomicroscopy

The biomicroscopy exam should be performed with the slit lamp using a beam width and intensity that provide optimal evaluation of the anterior segment.

This procedure will be the performed in the same manner for all subjects observed at the Investigator's site. The site will record all abnormal or present findings in the source document and the Investigator will evaluate the abnormal or present findings as non-clinically significant (NCS) or clinically significant (CS). CS and NCS abnormal findings will be recorded in the source documentation. However, only CS abnormal descriptions will be captured in the eCRF.

Anterior Chamber Cells	0 = No cells seen 1 = 1-5 cells 2 = 6-15 cells 3 = 16-30 cells 4 = > 30 cells
Anterior Chamber Flare	0 = None 1 = Mild (trace to clearly noticeable, visible) 2 = Moderate (without plastic aqueous humor) 3 = Marked (with plastic aqueous humor) 4 = Severe (with fibrin deposits and/or clots)
Eyelid • Eyelid Hyperemia • Eyelid Edema	0 = None 1 = Mild 2 = Moderate 3 = Severe
Conjunctiva • Edema (Chemosis) • Conjunctival Discharge/Exudate	0 = None 1 = Mild 2 = Moderate 3 = Severe
Corneal Edema	0 = None 1 = Mild 2 = Moderate 3 = Severe
Corneal Endothelium	0 = Normal 1= Abnormal (pigment, keratoprecipitates, guttata)
Iris	0 = Normal 1 = Abnormal
Pupil	0 = Normal 1 = Abnormal
Lashes	0 = Normal 1 = Abnormal
Lens	0 = Normal 1 = Abnormal

12.11 Appendix 11: Intraocular Pressure (IOP)

Intraocular pressure must be measured (mmHg) by Goldmann Applanation tonometry with every effort to ensure the same examiner using the same tonometer for all visits.

12.12 Appendix 12: Dilated Ophthalmoscopy

This procedure will occur after instillation of dilating drops and upon Investigator confirmation that **both eyes** are fully dilated (recommended time of 20 minutes). As dilating drops will be instilled, dilated ophthalmoscopy must be performed after Pinhole Distance VA, IOP, and assessments of corneal staining and healing. Dilated ophthalmoscopy will include assessment of the vitreous, retina, macula, choroid, optic nerve, and vertical optic nerve cup-to-disc ratio. After the ophthalmoscopy procedure, the Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at screening, the Investigator will determine whether the abnormality would exclude the subject from study participation. All abnormalities should be noted in the source and clinically significant or non-clinically significant should be marked.

12.13 Appendix 13: Drop Comfort Assessment

At Visits 2 and 6, ask the subject to rate the comfort of the drop for both eyes as one score at 1 minute and 5 minutes post-dose.

COMFORT/TOLERABILITY OF INVESTIGATIONAL PRODUCT
Overall Comfort of Investigational Product: 0=Comfortable and 10=Uncomfortable
0 5 10 |_____|

12.14 Appendix 14: Investigator Agreement

A Phase 2, Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Dose-Response, Parallel-Group Study of SY-201 Ophthalmic Solution versus Vehicle Control in Subjects with Dry Eye Disease

Version No.: 1.2

Issue Date: 13 April 2022

I have read the clinical study protocol and understand it. I agree to conduct the study as outlined in this document and in accordance with Good Clinical Practice Guidelines, all local and federal requirements and regulations, and in compliance with those precepts set forth in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

Further, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

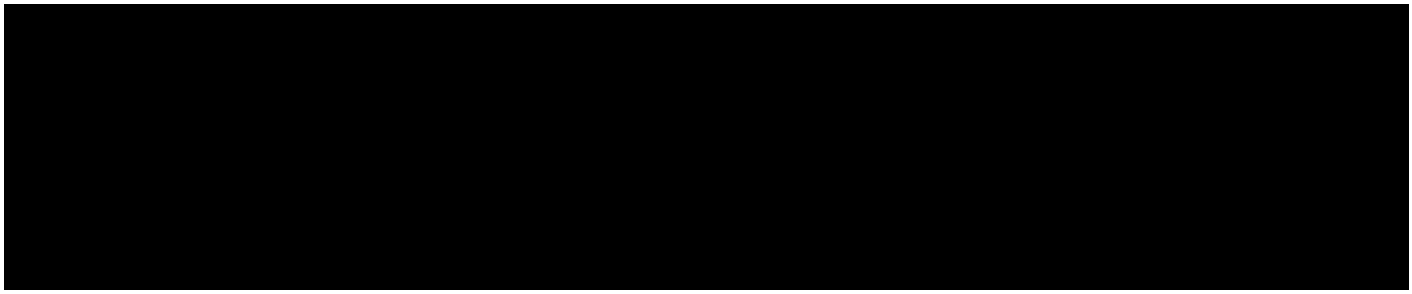
Signature of Investigator:

12.15 Appendix 15: Compliance Statement

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and as stipulated in the Declaration of Helsinki (2013) with respect to the use of human subjects in clinical studies and investigations.

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously a roved consent form.



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