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Clinical Study SY201-CS201
Statistical Analysis Plan
28 November 2023

Statistical Analysis Plan for 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

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SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
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
BID	Twice daily
BOCF	Baseline observation carried forward
BUN	Blood urea nitrogen
CCLRU	Cornea and Contact Lens Research Unit
CFB	Change from baseline
CFR	Code of Federal Regulations
CFS	Corneal fluorescein staining
CMP	Clinical Monitoring Plan
CMs	Concomitant medications
CRF	Case report form
CS	Clinically significant
DED	Dry eye disease
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
[redacted]	
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational product

IPL	Intense pulsed light
IRB	Institutional Review Board
IUD	Intra-uterine device
[redacted]	
LOCF	Last observation carried forward
LogMAR	Logarithm of the Minimum Angle of Refraction
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MMP-9	Matrix metalloproteinase-9
MMRM	Mixed-model repeated measures
mNEI	Modified National Eye Institute (scale)
NCS	Non-clinically significant
NEI	National Eye Institute
OU	Oculus uterque (both eyes)
POC	Point-of-care
PP	Per Protocol
PT	Preferred term
QC	Quality control
RBC	Red blood cell count
RDW	Red cell distribution width
SAE	Serious adverse event
[redacted]	
SD	Standard deviation
SE	Study eye
SOC	System organ class
SOP	Standard Operating Procedure
TBUT	Tear film break-up time

tCFS	Total corneal fluorescein staining
TEAE	Treatment emergent adverse event
UPT	Urine pregnancy test
[redacted]	
WBC	White blood cell count
WOCBP	Women of childbearing potential
WHODrug	World Health Organization Drug Dictionary

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) <u>Secondary Efficacy Endpoints</u> <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. 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 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. 7. Are considered legally blind in either eye (LogMAR BCVA ≥1.0 or Snellen BCVA ≤20/200). 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 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:	Efficacy • 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 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. 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) • 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 will be used. [redacted]

	[redacted] Subgroup analyses will be based on MMP-9 level (elevated or normal) 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.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

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.

Figure 1 summarizes the design of the study.

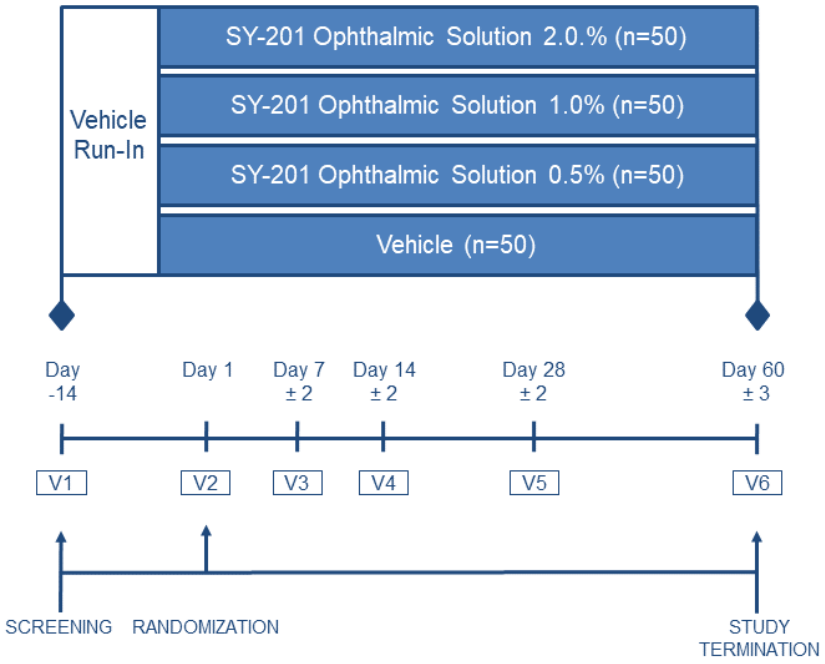

Figure 1: Study Schematic

9.5.1.1. Visit and Procedure Schedule

See Table 1 in Appendix I for a complete visit and procedure schedule.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), sex, race, and ethnicity will be collected at Visit 1. Baseline disease characteristics include tCFS score (mNEI scale),

9.5.1.2.2. Medical and Surgical History

Ocular and non-ocular medical history will be collected at Visit 1.

9.5.1.2.3. Prior and Concomitant Medications

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).

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.

Restricted and prohibited prior and comcomitant therapy are outlined in the protocol Section 5.5.1.

9.5.1.3. Efficacy Assessments

9.5.1.3.1. Primary Efficacy Assessment(s)

Corneal staining will be assessed at each in-clinic visit. The modified National Eye Institute (mNEI) scale defines 5 regions (central, superior, temporal, nasal, and inferior) of the eye and assigns a score of 0-4 to each region in increments of 0.5 to assess the severity of corneal staining. The sum of the 5 regions provides the total score.

9.5.1.3.2. Secondary Efficacy Assessments

9.5.1.3.3. Exploratory Efficacy Assessments

Not applicable.

9.5.1.4. Safety Assessments

The safety of SY-201 Ophthalmic Solution will be evaluated using the following assessments, conducted at each in-clinic visit unless otherwise noted.

1. Adverse event (AE) monitoring
2. Safety labs (chemistry and hematology) – Visits 1 and 6
3. Best Corrected Visual Acuity (BCVA)
4. Slit lamp biomicroscopy and external eye exam
5. Intraocular pressure (IOP)
6. Dilated ophthalmoscopy – Visits 1 and 6
7. Drop comfort assessment – Visits 2 and 6

9.5.1.4.1. Adverse Events

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.

Severity of AEs is described with the following scale:

- **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 to study intervention is classified according to the following scale:

- **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.

9.5.1.4.2. Safety Labs (Chemistry and Hematology)

The following clinical laboratory tests will be performed at Visits 1 and 6.

- 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

9.5.1.4.3. Best Corrected Visual Acuity (BCVA)

The BCVA is measured on both eyes in LogMAR at every in-clinic visit. LogMAR is calculated as Baseline value + (n × 0.02); where the baseline value is the LogMAR number of the last line read (at least one letter read correctly in this line), "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.

9.5.1.4.4. Slit Lamp Biomicroscopy and External Eye Exam

The biomicroscopy exam should be performed at every in-clinic visit 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 and flare will be graded on 5-point scales. Eyelid hyperemia and edema, corneal edema, and conjunctival edema (chemosis) and discharge/exudate will be graded on a 4-point scale (None, Mild, Moderate, Severe).

Normality for iris, pupil, lashes, lens, and corneal endothelium will be collected.

9.5.1.4.5. Intraocular Pressure (IOP)

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

9.5.1.4.6. Dilated Ophthalmoscopy

Dilated ophthalmoscopy will be completed at Visits 1 and 6 and will include assessment of the vitreous, retina, macula, choroid, optic nerve, and vertical optic nerve cup-to-disc ratio. Findings will be graded as normal or abnormal. All abnormalities will be recorded in the source documentation and CS or NCS will be indicated. Clinically significant abnormal findings will be reported in the medical history or adverse event eCRF.

9.5.1.4.7. Drop Comfort Assessment

At Visits 2 and 6, subjects will be asked to rate the comfort of the drop for both eyes as one score at 1 minute and 5 minutes post-dose. Integer scores range from 0 (Comfortable) to 10 (Uncomfortable).

9.5.2. Appropriateness of Measurements

All assessments used in this study are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3. Primary Efficacy Variable(s)

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)

9.5.4. Drug Concentration Measurements

No drug concentration measurements will be made for this study.

9.6. DATA QUALITY ASSURANCE

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.

9.6.1. Training and Education of Investigators and Study Site Personnel

An Investigator Meeting will be held before study initiation and attended by the Investigators and/or Sub-Investigators from each study site, study coordinators from each study site, if possible, and personnel from the sponsor and the Contract Research Organization (Lexitas Pharma Services, Inc., hereafter referred to as Lexitas). The purpose of this meeting is to train and instruct the Investigators and the study coordinators on the proper conduct of the clinical trial and ensure that all subjects are aware of their obligations set out by the protocol, ICH guidelines, GCP guidelines, and other applicable regulatory requirements.

9.6.2. Monitoring of Study Sites

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.

This clinical trial will be monitored at regular intervals. All information dealt with during these visits will be treated as strictly confidential. All monitoring and study management will be conducted according to GCP and United States Code of Federal Regulations.

9.6.3. Data Entry and Verification of Database Used for Analysis and Reporting

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.

Lexitas will review the eCRFs entered by investigational site staff for completeness and accuracy and instruct the investigational site staff to make any required corrections or additions. After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Queries will be sent to the investigational site and designated investigational site staff are required to respond to the query and edit data, as necessary. All changes to the study database will be documented.

It is the responsibility of the monitor to make certain that all data are completed on the eCRFs. At the end of each study period, the Investigator will sign and date the eCRF to attest to the authenticity of the collected data and coherence between the data in the eCRF and the data in the source documents.

9.6.4. Clinical Study Report

The final clinical study report will be reviewed, audited, and approved by medical, clinical, statistical, and regulatory staff from the sponsor, and key study contributors from Lexitas.

9.6.5. Inter-Laboratory Standardization Methods

Not applicable. A single, qualified, and certified central clinical laboratory will be used to analyze and report clinical laboratory data.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

This section of the analysis plan describes the analyses explicitly mentioned in the protocol as well as additional analyses not explicitly mentioned in the protocol but planned prior to breaking the treatment mask. Section 9.8 describes any changes to analyses that were explicitly mentioned in the protocol or statistical analysis plan.

9.7.1. Statistical and Analytical Plans

General Conventions

Summary statistics for the data collected during this study will be presented to give a general description of the subjects studied. Data from all sites will be combined in the computation of these descriptive summaries. Categorical variables will be summarized by the frequency and percentage of subjects in each category. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values.

Number of subjects, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, standard deviations, and quartiles will be calculated to one more decimal place than the source data. Percentages will be calculated to the nearest one decimal place. Zero count cells will be displayed as "0" with percentage of (0%). Unless otherwise noted, summaries will be performed by the treatment group and presented in the order of: SY-201 2.0% or 1.0% or 0.5% (efficacy analyses only), SY-201, 2.0%; SY-201, 1.0%; SY-201, 0.5%; Vehicle.

Statistical tests will be presented as two-sided p-values rounded to four decimal places; p-values less than 0.0001 will be presented as '<0.0001' and p-values = 1 will be presented as '>0.9999' in all tables. Unless otherwise indicated, statistical testing will be carried out at the $\alpha = 0.05$ significance level.

Baseline values will be defined as the last measurement prior to dosing of double-masked study medication. Ocular measurements will use the most recent measurement for each eye.

Numeric laboratory data may be recorded at limits of detection (with a '<' or '>' sign, i.e. < 0.1 or > 0.1). To summarize the data, the original value will be converted to one unit less or more at the level of measured precision (e.g. 0.4 in the case of < 0.5 and to 0.6 in the case of > 0.5). The actual values will be presented in the data listings.

MMP-9 data may be recorded at limits of detection of < 5 ng/mL or > 1000 ng/mL. To summarize the data, the original value will be converted to either 4 ng/mL or 1010 ng/mL, respectively. The actual values will be presented in the data listings.

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

Computations for all results will be performed using SAS (Version 9.4, SAS/STAT 15.2) computer software package (SAS Institute, Inc, 2013, 2020), unless otherwise specified.

Strata and Covariates

For analysis of efficacy endpoints, longitudinal models will model the change from baseline of each endpoint as the dependent variable with the baseline measurement of the corresponding endpoint as a covariate and treatment group as the main effect. A random effect for site will be added to account for site-to-site variability.

Subgroups

Subgroup analyses will include testing of the mean CFB in tCFS,

Subgroup analyses by sex and age group (<65 years, ≥65 years) may also be performed.

Multiplicity

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, . Should both endpoints achieve statistical significance for the 2.0% dose, testing w procee to Y-201 Ophthalmic Solution 1.0% versus Vehicle, first testing tCFS and, if statistically significant, . 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, . In other words, the first non-significant result in this testing hierarchy of six hypotheses will imply that subsequent tests are non-significant.

Missing Data and Outliers

Every attempt will be made to capture all study data. All analyses will utilize observed data only. Analysis of continuous efficacy endpoints using MMRM assumes missing at random (MAR). Sensitivity analyses of the primary endpoints will be performed utilizing control-based pattern imputation, last observation carried forward (LOCF), and baseline observation carried forward (BOCF).

Visit Windows

The nominal visits listed in the eCRF will be used in the summaries. In general, unscheduled visits will not be summarized in tables unless otherwise noted.

Missing Dates

Missing dates that occur for prior or concomitant medications or adverse events will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, if the given year (or year-month) is the same as study drug administration, the start date will be imputed as study drug administration date; otherwise, missing month-day (or day) will be imputed as '01-01' (or '01').
- For stop dates, missing months will be imputed as '12' and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

Imputed dates will only be used to classify events or medications, such as occurring before or after the start of treatment. Imputed dates will only be used in tables. Listings will display the available date data.

Interim Analysis

There is no unmasked efficacy or futility interim analysis for this study.

9.7.1.1. Analysis Populations

9.7.1.1.1. 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.

The Safety Analysis Set will include all subjects who took at least one dose of double-masked 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). If the safety analysis set is the same as the FAS, then safety results will be provided using the FAS.

9.7.1.1.2. Analysis Eyes

Subjects in the FAS will have at least one eye that qualifies based on the criteria in the protocol. Both eyes may qualify based on the criteria.

Efficacy analyses will be performed in the study eye and non-study eyes.

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.

Safety analyses will be presented for both eyes.

9.7.1.2. Analysis of Subject Disposition

The number of subjects randomized at each site will be summarized by treatment group and overall.

Subjects' enrollment and disposition during the study will be summarized by treatment group and overall using Randomized Subjects. The reasons for discontinuation will be displayed in the order as they appear on the eCRF.

The summary table will include the following. The percentages will be calculated based on the number of subjects randomized. For reason for discontinuation from study, percentages are based on the number of subjects who discontinued the study.

- Number of subjects screened
- Number and percentage of subjects randomized
- Number and percentage of subjects randomized with any protocol deviation
- Number and percentage of subjects treated
- Number and percentage of subjects treated with any protocol deviation
- Number and percentage of subjects in the Safety, Full, and Per Protocol Analysis Sets
- Number and percentage of subjects treated who completed the study
- Number and percentage of subjects treated who discontinued from the study
- The reasons for study discontinuation
- Number and percentage of subjects attending each scheduled study visit.

A listing of subjects who do not meet all inclusion criteria or meet exclusion criteria will be provided.

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), age group (<65 years, ≥65 years), sex, race, ethnicity, qualifying eyes (1 or 2), study eye (OD/OS), and baseline tCFS score

MMP-9, and

will be summarized descriptively by treatment group and overall using the FASand Safety Analysis Sets. For categorical parameters, the percentages will be calculated overall and based on the number of subjects in each treatment group based on non-missing observations. The baseline characteristic parameters will be summarized for both the study eye and the non-study eye if the assessments were done on each eye separately.

9.7.1.3.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 25.0, Mozzicato, 2009). The frequency and percentage of subjects with any medical history will be summarized by treatment group using the FAS. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within SY-201, 2.0%;
2. Descending frequency within SY-201, 1.0%;
3. Descending frequency within SY-201, 0.5%;
4. Descending frequency within Vehicle;
5. PT in alphabetical order.

The medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical history will be summarized separately. Ocular and non-ocular medical histories are identified according to which CRF the event is recorded. Ocular medical history will be summarized separately for study eye, non-study eye, and either eye.

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (Version 2022-03, Lagerlund et al., 2020) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of subjects with coded medications will be summarized by treatment group using the Safety Analysis Set. A subject who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup is sorted alphabetically, and preferred term is sorted by descending frequency overall within each Level 3 term according to:

1. Descending frequency within SY-201, 2.0%;
2. Descending frequency within SY-201, 1.0%;
3. Descending frequency within SY-201, 0.5%;
4. Descending frequency within Vehicle;
5. PT in alphabetical order.

Prior and concomitant medications will be summarized separately. Ocular medications are defined as those medications for which an eye has been specified (OD, OS, or OU). Ocular and non-ocular medications will be summarized separately. Ocular medications will be summarized separately for study eye, non-study eye, and either eye.

Prior medications are defined as any medications that started and stopped prior to the first dose of double-masked study drug. Concomitant medications are defined as any medications that (1) start prior to the first dose of double-masked study drug and stop or are ongoing at or after the date of first dose of double-masked study drug; or (2) start at or after the first dose of double-masked study drug. Medications taken after Visit 6 or withdrawal from the study are not considered concomitant.

9.7.1.4. Analysis of Study Medication Compliance and Exposure

The overall treatment compliance and exposure will be assessed by the data from the in-clinic administration, IP accountability, and study completion eCRFs and will be summarized by treatment group using the Safety Analysis Set.

The total number of doses of double-masked study drug that were taken will be calculated as the number of used vials returned to the clinic. Each single use vial contains product for one OU dose.

Treatment compliance for double-masked study drug is defined as the proportion of doses taken out of the expected number of doses for the double-masked treatment period. The overall compliance (%) will be calculated as (total number of doses taken / expected number of doses) × 100. The expected number of doses is defined as doses per day × days in double-masked treatment period, i.e., [2 × (last double-masked dose date - first double-masked dose date + 1)]. Last double-masked dose date will be taken from the study completion eCRF. Since the expected number of doses is based on last dose, compliance is adjusted for the early withdrawals. Treatment compliance for the run-in period is defined as (total number of doses taken / expected number of doses) × 100 where the expected doses are [2 × (Visit 2 date – Visit 1 date)].

Duration of exposure of double-masked study drug will be calculated as the total number of days from the first double-masked dose date to the last double-masked dose date plus 1 (one) regardless of temporary dose interruptions.

Total number of doses of double-masked study drug that were taken, compliance, and the duration of exposure to double-masked study drug (days) will be summarized by descriptive statistics. The frequency and percentage of subjects in the following study drug compliance categories (≥ 80%, < 80%) will be summarized by treatment group. The percentages will be calculated based on the number of non-missing observations in each treatment group of the Safety Analysis Set. No inferential statistics will be calculated.

Total number of doses of single-masked run-in drops taken, duration (in days), compliance, and compliance categories (≥ 80%, < 80%) during the run-in period will be summarized by treatment group based on Safety Analysis Set. No inferential statistics will be calculated.

9.7.1.5. Analysis of Efficacy

Summary descriptive statistics will be presented for all study visits at which efficacy data are collected. Efficacy analyses will be presented by the study eye and non-study eyes.

For subjects who discontinue treatment prior to Visit 6, data collected using Early Termination eCRFs will not be summarized separately unless the termination occurred on a scheduled visit (within the visit windows of a particular visit).

All longitudinal models will be fit using the MIXED procedure in SAS. Categorical analyses will be conducted using the FREQ procedure.

All efficacy analyses will be conducted using the FAS Analysis Sets.

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[redacted] and Vehicle, first testing tCFS and, if statistically significant, . Should both endpoints achieve statistical significance

for the [redacted] testing will proceed to SY-201 Ophthalmic Solution [redacted] versus Vehicle, first testing tCFS and, if statistically significant, [redacted]. Should both endpoints achieve statistical significance for the [redacted], testing will proceed to SY-201 Ophthalmic Solution [redacted] and Vehicle, first testing tCFS and, if statistically significant, [redacted]. In other words, the first non-significant result in this testing hierarchy of six hypotheses will imply that subsequent tests are non-significant.

Testing of all active doses combined compared to vehicle will also be performed.

9.7.1.5.1. Primary Efficacy Analysis

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 eye [redacted] using the FAS.

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

Endpoints: Change from baseline at Day 60 for tCFS using study eyes and change from baseline at Day 60 for eye dryness score.

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 eye dryness 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 a 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.

Sample repeated measures model code:

```
PROC MIXED DATA=indata;
 CLASS subject center visit treatment(REF='Vehicle');
 MODEL change = baseline_value visit treatment visit*treatment / Solution DDFM=KR;
 REPEAT visit / SUBJECT=subject TYPE=UN;
```

```
 RANDOM center;
 LSMEANS treatment*visit / slice = visit DIFF CL;
RUN;
```

If the model fails to converge using this covariance structure, spatial power or compound symmetry will be implemented in this order.

Sensitivity analyses of the primary endpoints will be performed utilizing control-based pattern imputation, last observation carried forward (LOCF), and baseline observation carried forward (BOCF).

Control-based pattern imputation would be performed using code similar to the below. The first call is to ensure a monotone missing data pattern. The second call is to perform the control-based pattern imputation.

```
PROC MI DATA=indata SEED= OUT=monotone MINIMUM=0 0 0 0 0 MAXIMUM=4 4 4 4 4 ROUND=0.5
NIMPUTE=25;
  MCMC IMPUTE = MONOTONE;
  VAR value_V2 value_V3 value_V4 value_V5 value_V6;
RUN;

PROC MI DATA=monotone SEED= OUT= MINIMUM=. 0 0 0 0 0 MAXIMUM=. 4 4 4 4 4 ROUND=0.5
NIMPUTE=1;
  by _imputation_;
  CLASS treatment;
  VAR value_V2 value_V3 value_V4 value_V5 value_V6;
  MONOTONE reg(/details);
  MNAR model(value_V3 value_V4 value_V5 value_V6 / modelobs= (treatment = 'vehicle'));
RUN;
```

Comparisons among individual arms will be obtained from the lsmeans statement. Comparisons between the combined SY-201 arm and Vehicle (least-squares means, treatment differences, 95% confidence intervals, and p-values) will be obtained using estimate statements. Assume treatments are ordered:

1. SY-201 2.0%;
2. SY-201 1.0%;
3. SY-201 0.5%;
4. Vehicle.

And visits 3, 4, 5, and 6 are ordered numerically. Let $n_{2.0\%}$, $n_{1.0\%}$, and $n_{0.5\%}$ be the total number of subjects for the appropriate arms in the respective analysis set (FAS or Per Protocol). Define $p_{2.0} = \frac{n_{2.0\%}}{n_{2.0\%}+n_{1.0\%}+n_{0.5\%}}$ with $p_{1.0}$ and $p_{0.5}$ defined similarly.

To generate the estimates for the combined SY-201 for Visit 3, see the below code for an example for Visit 3.

```
estimate 'SY-201 Average V3'
      intercept       1
      baseline        <<overall average at baseline for all subjects>>
      visit           1 0 0 0
      treatment       p2.0 p1.0 p0.5 0
```

```
      visit*treatment p2.0 p1.0 p0.5 0 0 0 0 0
                        0   0   0   0 0 0 0 0;

estimate 'SY-201 Average minus Vehicle V3'
      treatment       p2.0 p1.0 p0.5 -1
      visit*treatment p2.0 p1.0 p0.5 -1 0 0 0 0
                        0   0   0   0 0 0 0 0;
```

9.7.1.5.2. Secondary Efficacy Analyses

9.7.1.5.3. Exploratory Efficacy Analysis

Not applicable.

9.7.1.6. Analysis of Safety

Safety will be evaluated by:

1. Adverse event (AE) monitoring
2. Safety labs (chemistry and hematology)
3. Best Corrected Visual Acuity (BCVA)
4. Slit lamp biomicroscopy and external eye exam
5. Intraocular pressure (IOP)
6. Dilated ophthalmoscopy
7. Drop comfort assessment

The Safety Analysis Set will be used for all safety analyses. All data will be summarized as observed, and no data imputation will be performed. No statistical treatment group comparisons

will be performed, unless otherwise specified. Analyses will be presented by study eye and non-study eye, if applicable.

9.7.1.6.1. Adverse Events

AEs are coded using MedDRA Version 25.0. Treatment-emergent adverse events (TEAE) are defined as events that start on or after the first dose administration of double-masked study medication up to and including the last dose of double-masked study medication plus 30 days. Pretreatment adverse events are events that begin prior to first dose administration of double-masked study medication. Ocular AEs are defined as those events for which an eye has been specified (OD, OS, or OU).

Ocular and non-ocular TEAEs will be summarized separately. Ocular TEAEs will be presented by study eye and non-study eye and overall (OU) if an event occurs in either eye.

In all summaries of TEAEs, percentages are calculated based on the number of subjects in each treatment group of the Safety Analysis Set.

Overall summaries of TEAEs by treatment will include:

- the number of TEAEs and serious TEAEs reported;
- the number and percentage of subjects who experienced any TEAE;
- the number and percentage of subjects who experienced any serious TEAE and the reason for seriousness;
- the number and percentage of subjects with any TEAE by worst severity and worst relationship.
- the number and percentage of subjects with any TEAEs leading to discontinuation of double-masked study drug;
- the number and percentage of subjects with any TEAEs leading to study termination.

Summaries of the frequency and percentage of subjects with TEAEs by SOC and preferred term by treatment group will include:

- All TEAEs by SOC and preferred term;
- All TEAEs by SOC, preferred term, and maximum severity;
- All TEAEs by SOC, preferred term, and maximum relationship.

System organ class (SOC) will be sorted alphabetically, and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within SY-201, 2.0%;
2. Descending frequency within SY-201, 1.0%;
3. Descending frequency within SY-201, 0.5%;
4. Descending frequency within Vehicle;
5. PT in alphabetical order.

Subjects are counted only once for each SOC and PT. In summaries of maximum severity and maximum relationship, subjects with multiple occurrences of events will only be counted once at the maximum severity/relationship per SOC and PT.

Any treatment-emergent AEs that have a missing severity will be presented as severe in the summary table but will be presented with a missing severity in the data listing. Any treatment-emergent AEs that have a missing relationship will be presented as "Related" in the summary table but will be presented with a missing relationship in the data listing.

All AEs are displayed in listings. In addition, separate listings will be provided for:

- Subjects with any treatment-emergent adverse event leading to study drug discontinuation or study termination;
- Subjects with any serious adverse event (treatment-emergent or otherwise);
- Subject deaths.

9.7.1.6.2. Safety Labs (Chemistry and Hematology)

Descriptive summaries of the observed test results at Visits 1 and 6 as well as the change from baseline at Visit 6 will be presented for serum chemistry and hematology labs. The frequency and percentage of subjects with observed values of Low, Normal, High as well as the categorical shift from baseline at Visit 6 will be tabulated. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Analysis Set.

It is expected that all samples will be analyzed by a central laboratory. If a local laboratory is used (such as for an unscheduled visit), the results will be included in the listings of laboratory data, but will not be included in descriptive summaries.

The results of pregnancy tests for women of childbearing potential will be presented in a listing.

9.7.1.6.3. Best Corrected Visual Acuity (BCVA)

Descriptive summaries of the observed values of LogMAR at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes. A categorical analysis of subjects who lose 0.3 lines ETDRS in either eye at each visit will be conducted.

9.7.1.6.4. Slit Lamp Biomicroscopy and External Eye Exam

The frequency and percentage of subjects with observed values of each categorical response or grade as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Analysis Set.

9.7.1.6.5. Intraocular Pressure (IOP)

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes. A categorical analysis of subjects who gain 10 mmHg or more in IOP at each visit will be conducted.

9.7.1.6.6. Dilated Ophthalmoscopy

The frequency and percentage of subjects with observed values of each categorical response at Visits 1 and 6 as well as the categorical shift from baseline at Visit 6 will be tabulated for both eyes. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Analysis Set.

Descriptive summaries of the observed cup-to-disc ratio at Visits 1 and 6 as well as the change from baseline at Visit 6 will be presented for both eyes.

9.7.1.6.7. Drop Comfort Assessment

Descriptive summaries of the observed values at Visits 2 and 6 at 1 minute and 5 minutes post-dose will be presented.

9.7.2. Determination of Sample Size

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.

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. Protocol Amendments

Not applicable.

9.8.2. Changes from Protocol-Specified Analyses

Time to first use of artificial tears will not be performed.

9.8.3. SAP Amendments

The SAP was amended to modify the MMP-9 subgroup analyses to be based on baseline tCFS. A Per Protocol Analysis Set will not be defined.

REFERENCES

1. Mozzicato P. (2009). MedDRA: An overview of the medical dictionary for regulatory activities. Pharmaceutical Medicine 23: 65-75.
2. Lagerlund O, Strese S, Fladvad M & Lindquist M. (2020). WHODrug: A global, validated and updated dictionary for medicinal information. Therapeutic Innovation & Regulatory Science 54: 1116–1122.
3. SAS Institute Inc. What's New in Base SAS® 9.4 and SAS® Viya®. (2013). SAS Institute Inc., Cary, NC, USA.
4. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

APPENDIX I: SCHEDULE OF ASSESSMENTS

Table 1: Schedule of 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 Schirmer test.

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

[redacted]

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i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

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