Statistical Analysis Plan for Study 2007-301-005

A Multicenter, Single-masked, Randomized Study to Compare the Efficacy and Safety of a New Artificial Tear Formulation (011516X) with Systane® Ultra Multidose for 90 Days in Participants with Dry Eye Disease

Date: 2 August 2021

Version Amendment 1

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1.0 Introduction

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the final Protocol 2007-301-005 Amendment 2 dated 08 Jun 2020. Specifications of tables, figures, and data listings are contained in a separate document.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

The overall study purpose is to compare the efficacy and safety of a new artificial tear formulation (011516X) with Systane Ultra multidose in participants with dry eye disease (DED).

2.1.1 Objectives and Measures

Table 2-1 provides each objective and endpoint under the associated statistical analysis categories.

Table 2-1 Objectives and Measures

Objectives	Measures
Efficacy	
To evaluate the efficacy of 011516X in participants with signs and symptoms of DED compared with Systane Ultra MD	**Primary Efficacy**
	Total staining (sum of corneal and conjunctival staining)
	Secondary Efficacy
	Current Symptom Survey
	Other Efficacies
	• Corneal staining (modified National Eye Institute [NEI] grading scheme, with fluorescein) • Conjunctival staining (modified NEI grading scheme, with lissamine green) • Tear break-up time (TBUT, with fluorescein) • Schirmer test (with anesthesia) • Ocular Surface Disease Index© (OSDI) • Study Eye Drop Experience and Tolerability Questionnaire • Functional Vision Questionnaire

	• 5-Minute Blurry Vision and Ocular Discomfort Questionnaire
Safety	
To evaluate the safety of 011516X in participants with signs and symptoms of DED compared with Systane Ultra MD	• AEs • Slit-lamp biomicroscopy • Currently corrected distance visual acuity • Best-corrected distance visual acuity (BCDVA) • Intraocular pressure (IOP) (participants with glaucoma or ocular hypertension [OHT] only)

2.1.2 Statistical Hypotheses

The null and alternative hypotheses for the primary efficacy endpoint are:

Noninferiority

- H_0: $\mu_{011516X} - \mu_{Systane\ Ultra} \geq 2.3$
- H_A: $\mu_{011516X} - \mu_{Systane\ Ultra} < 2.3$

Superiority

- H_0: $\mu_{011516X} - \mu_{Systane\ Ultra} \geq 0$
- H_A: $\mu_{011516X} - \mu_{Systane\ Ultra} < 0$

2.2 Study Design Overview

This study is designed as a multicenter, single-masked, randomized, 2-arm, parallel-group study comparing the efficacy and safety of a 011516X with Systane Ultra MD (see Figure 2-1). After a 7-days a run-in period, if still qualified at the Day 1 (Baseline) visit, participants will then be randomized in a 1:1 ratio to use 011516X or Systane Ultra MD. Participants will be instructed to instill 1 to 2 drops of their assigned study intervention (investigational eye drops) in each eye, 3 times per day for approximately 90 days. The

primary efficacy measure is total ocular staining and the primary analysis timepoint is at Day 90.

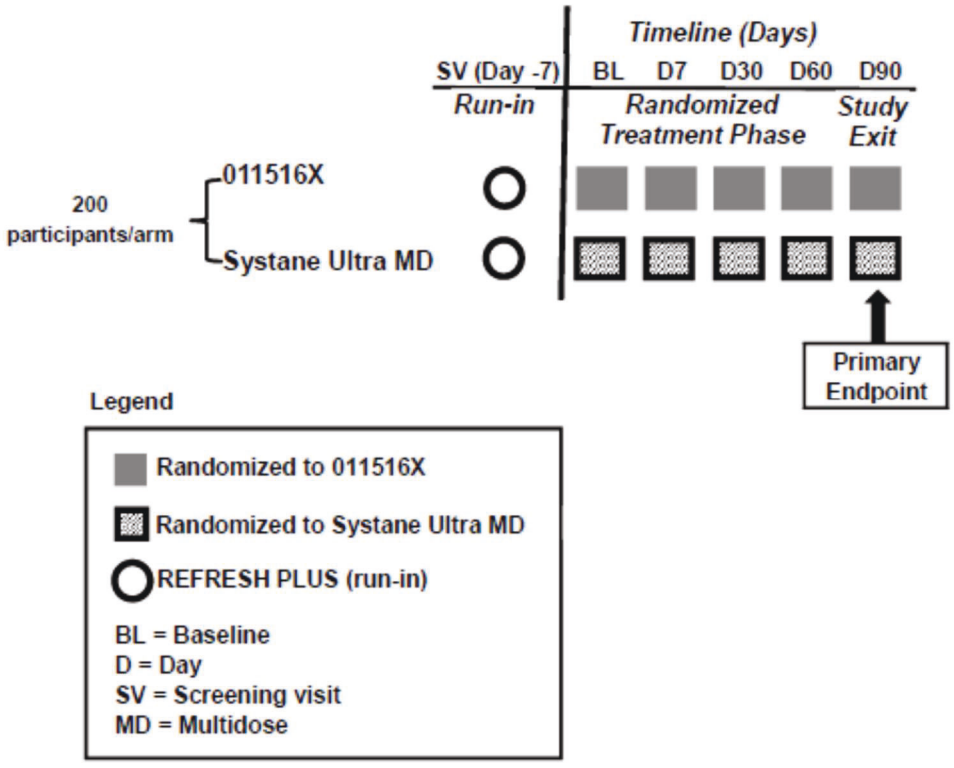
Approximately 400 participants (200 participants in each arm) will be enrolled at approximately 28 sites in the US in order to have 340 participants (170 participants in each arm) complete the study through Day 90, assuming an approximate 15% dropout rate. Participants who prematurely discontinue from the study will not be replaced.

No interim analyses are planned for this study.

2.2.1 Schema

The schematic of the study is shown in Figure 2-1.

Figure 2-1 Study Schematic



2.3 Treatment Assignment and Masking

This study will use a 1:1 treatment allocation to 011516X or Systane Ultra MD, with a central stratification by Day 1 (Baseline) total ocular staining score in the study eye (mild/moderate = score of 6 to 25 vs severe = score of 26 to 43). The study eye is defined as the worst eye based on total ocular staining score at Day 1 (Baseline). If both eyes have the same total ocular staining score, the right eye will be designated as the study eye.

Prior to initiation of study intervention, each participant who provides informed consent will be assigned to a participant number through an automated IxRS that will serve as the participant's identification number on all study documents. Participant numbers will be assigned in ascending order across all sites and should not be omitted or reused.

At the end of the Screening (Day -7) visit, all eligible participants will receive a run-in medication kit (REFRESH PLUS) for use during the 7-day run-in period. Sites will dispense the run-in medication kit according to the IxRS instructions.

At the end of the Day 1 (Baseline) visit, all eligible participants will be stratified by their Day 1 (Baseline) study eye total ocular staining score and be randomly assigned to 1 of 2 treatment arms in a 1:1 ratio based on a randomization scheme prepared by Allergan Biostatistics. This will require the delegated site personnel to enter the participant's Screening Visit (Day -7) and Baseline (Day 1) total corneal and conjunctival staining scores of each eye directly into IxRS. IxRS will then determine which eye is the study eye and assign the participant to a stratification group and a treatment arm, thus providing the site with the specific study intervention kit assignment. Sites will dispense study intervention according to the IxRS instructions.

2.4 Sample Size Determination

The primary efficacy variable is change from baseline in total staining score at Day 90. Based on the assumption of noninferiority test for a between-group difference (ie, the

noninferiority margin) of 2.3 units in mean change from baseline in total staining at Day 90 with no inherent treatment difference with common standard deviation of 6.01, 170 participants will be required in each intervention group to detect the above intervention difference with a power of 90% or greater at the 1-sided 2.5% significance level. Assuming a 15% dropout rate, 200 participants will be randomized for each arm with a total of 400 participants to achieve the required sample size at Day 90.

3.0 Endpoints

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as change from baseline in total staining score (sum of corneal and conjunctival staining scores) of study eye at Day 90.

3.2 Secondary Efficacy Endpoint

The secondary endpoint is defined as change from baseline in Current Symptom Survey total score (composite of all symptoms) at Day 90.

3.3 Other Exploratory Efficacy Endpoints

Other efficacy endpoints are listed below.

- Change from baseline in corneal staining score
- Change from baseline in conjunctival staining score
- Change from baseline in total staining score other than Day 90
- Change from baseline in Current Symptom Survey total score (composite of all symptoms) other than Day 90
- Change from baseline in individual symptom scores from Current Symptom Survey
- Change from baseline in Schirmer test
- Change from baseline in TBUT
- Change from baseline in OSDI
- Change from baseline in Functional Vision Questionnaire, 5-Minute Blurry Vision, and Ocular Discomfort Questionnaire
- Study Eye Drop Experience and Tolerability Questionnaire

Additional endpoints, such as responder proportions, can be added based on the study team requests.

3.4 Safety Endpoints

The safety variables include the study drug exposure, AEs, and results from the following assessments (Appendix B):

- Slit-lamp biomicroscopy
- Currently corrected distance visual acuity
- BCDVA
- IOP (participants with glaucoma or OHT only)

4.0 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 4-1 Analysis Populations

Population	Definition	Treatment Used for Analysis
Intent-to-treat (ITT)	Participants who are randomized	As randomized
Per-protocol (PP)	Randomized participants who have no protocol deviations affecting the primary efficacy analysis	As randomized
Safety	Treated participants who receive/take ≥ 1 administration of randomized study treatment	Actual received

Efficacy analyses will be done using the ITT population. Safety data analyses will be done using the safety population. The primary efficacy endpoint will also be done using for PP population.

Demographics and baseline characteristics will be done using the ITT population. Study drug duration, medical and surgical history, ophthalmic medical and surgical history, prior and concomitant medication will be done using the safety population.

The study eye is defined as the worst eye based on total ocular staining score at Day 1 (Baseline). If both eyes have the same total ocular staining score, the right eye will be designated as the study eye. The other eye will be the fellow eye.

5.0 Participant Disposition

Participant disposition encompasses the distribution of participants who enter the run-in period, get randomized, complete, and discontinue the 90-day randomized treatment period.

The summary of study disposition will be provided for the following:

- Number of participants in the run-in period
- Number of participants who fail to be randomized
- Number of participants randomized (this frequency count will be used as the denominator to calculate the percentages described below)
- Number and percentage of participants treated
- Number and percentage of participants who completed the study
- Number and percentage of participants who discontinued the study

6.0 Study Drug Duration

The study will consist of a 90-day treatment period. The treatment duration in days will be summarized using descriptive statistics by treatment group for the safety population.

The treatment duration will be calculated as last treatment date - first treatment date + 1.

The number and percentage of participants with each treatment duration (days) of ≥ 1, ≥ 7, ≥ 30, ≥ 60, and ≥ 90 will be summarized.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

7.1 Demographics and Baseline Characteristics

Demographic parameters (age, sex, race, ethnicity) will be summarized descriptively by treatment group for the ITT population.

7.2 Medical and Surgical History

Medical and surgical histories will be collected at visits of screening and Day 1. They will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher.

The number and percentage of participants with medical and surgical history in each primary system organ class and preferred term will be summarized by treatment group for the safety population.

7.3 Ophthalmic Medical and Surgical History

Ophthalmic medical and surgical histories will be collected at visits of screening and Day 1. They will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher.

The number and percentage of participants with ophthalmic medical and surgical history in each system organ class and preferred term will be summarized by treatment group for the safety population.

7.4 Prior and Concomitant Medications

The medication data will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced Version.

Prior medication is defined as any medication taken prior to the start of first randomized study treatment regardless of stop date of the medication. Concomitant medication is

defined as any medication taken on and after the start of first randomized study treatment regardless of the start date of the medication.

Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical code (4th level, or most specific level available if 4th level is unavailable).

The number and percentage of participants reporting prior or concomitant medications will be summarized further by ATC class and code, and preferred drug name. If more than one medication is coded to the same preferred drug name for the same participant, the participant will be counted only once for that preferred drug name. Prior and concomitant medications will be summarized by treatment group for the safety population, separately.

8.0 Efficacy Analyses

8.1 General Considerations

The following are general considerations for efficacy analyses:

- The efficacy analyses will be based on the ITT populations.
- Baseline is defined as the last non-missing assessment prior to the first dose of the single-masked study treatment.
- The change from baseline value will be computed as the postbaseline value minus the baseline value.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max).
- Categorical variables will be summarized by number of participants with observed values or events and percentages based on the specified population.
- All statistical analyses will be performed using SAS version 9.4 or higher.

8.2 Handling of Missing Data

Efficacy analyses will be based on observed data only.

8.3 Primary Efficacy Endpoint and Analyses

8.3.1 Primary Efficacy Endpoint

The primary efficacy variable is defined as the change from baseline in total staining score at Day 90.

8.3.2 Primary Efficacy Analysis

The primary efficacy analysis will be performed upon the ITT population using mixed effects repeated measures (MMRM) method. The difference and the 95% confidence interval will be constructed with the least squares means from the MMRM model with

treatment, visit, visit-by-treatment interaction, baseline total staining stratum, and baseline total staining stratum-by-visit interaction as the fixed effects. An unstructured covariance matrix will be selected for the repeated measure covariance.

In order to control the overall type I error rate in the primary efficacy analysis, the sequential procedures will be performed. Under this procedure, the noninferiority test will be performed first and the superiority test will be performed next only if the null hypothesis of noninferiority is rejected. To test the hypothesis of noninferiority, a 2-sided 95% confidence interval (CI) will be constructed for the difference in the mean change from baseline in total staining at Day 90. If the upper limit of 2-sided CI for the treatment difference (011516X minus Systane Ultra MD) is less than 2.3 units, then the 011516X tear formulation will be considered noninferior to Systane Ultra MD. If the upper limit of the aforementioned 2-sided CI is less than 0 units, then the 011516X tear formulation will be considered superior to Systane Ultra MD. Details of this procedure will be found in Section 12.0.

8.3.3 Sensitivity Analyses

Sensitivity analyses will be based on the PP population applying the primary efficacy analytical approaches.

8.4 Secondary Efficacy Analyses

The secondary efficacy variable will be analyzed with the same model described for the primary efficacy analysis in Section 8.3.2. The difference and the 95% CI will be constructed.

8.5 Exploratory Efficacy Analyses

Total staining score other than Day 90, Current Symptom Survey total score (composite of all symptoms) other than Day 90, individual symptom scores from Current Symptom

Survey, corneal staining score, and conjunctival staining score will be analyzed with the same method described for the secondary efficacy analysis in Section 8.3.2.

All other efficacy analyses will be performed to provide descriptive statistics. Summaries of the 011516X and Systane Ultra MD at each scheduled visit will be performed on Schirmer test, TBUT, Functional Vision Questionnaire, and Study Eye Drop Experience and Tolerability Questionnaire.

8.5.1 5-Minute Blurry Vision and Ocular Discomfort Questionnaire

The 5-Minute Blurry Vision and Ocular Discomfort Questionnaire will provide an assessment of blurry vision and ocular discomfort, each on a 0-100 scale. The assessment will be conducted at Day 1 and Day 90/Early Exit. At each visit, measurements will be collected before instillation of one drop to each eye (Baseline), and at post dose time points of 30 seconds, 1 minute, 90 seconds, 2 minutes, 3 minutes, 4 minutes, and 5 minutes. Change from baseline is calculated for each time point minus the pre-dose score of the same day. Change from baseline is only calculated for measurements within the same day.

8.6 Efficacy Subgroup Analyses

The primary efficacy variable will be analyzed by the stratification factor, Day 1 (Baseline) total ocular staining score in the study eye:

- mild/moderate = total ocular staining score of 6 to 25, and
- severe = total ocular staining score of 26 to 43.

9.0 Safety Analyses

9.1 General Considerations

The following are the general considerations for safety analyses:

- Safety analyses will be performed based on the safety population by treatment group.
- Baseline for safety endpoints is defined as the last non-missing assessment prior to the first dose of the single-blind treatment.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max).
- Categorical variables will be summarized by number of participants with observed values or events and percentages based on the specified population.
- AEs will be coded using MedDRA version 23.0 or higher.

9.2 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

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 treatment.

9.2.1 Treatment-emergent Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of randomized study treatment. However, an AE that occurs more than 30 days after the last dose of randomized study treatment for participants will not be counted as a TEAE.

An AE will be considered a treatment-emergent serious AE (TESAE) if it is a TEAE that additionally meets any SAE criterion.

9.2.2 Adverse Event Overview

Overall summary of TEAEs will be provided on a per-participant level for TEAEs, treatment-related TEAEs, TESAEs, deaths, and TEAEs leading to study treatment discontinuation.

9.2.3 Treatment-emergent Adverse Events by SOC and/or PT

The number and percentage of participants with TEAEs will be tabulated by primary system organ class (SOC) and preferred term (PT).

The number and percentage of participants with TEAEs will be tabulated by primary SOC, preferred term, and severity. If more than one event is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the greatest severity for the summarization by severity. If the severity of a TEAE is missing, the maximum severity will be assigned to the event for the summarization by severity. The value will be displayed as missing in the data listing.

The number and percentage of participants with treatment-related TEAEs will be tabulated by primary SOC and preferred term; and by primary SOC, preferred term, and relationship. If the relationship to the treatment is missing for a TEAE, the event will be considered related to the treatment for the summarization. The value will be displayed as missing in the data listing.

Ocular treatment-emergent AEs will also be summarized. An ocular TEAE will be defined by the location information on the adverse event page in the eCRF. Ocular treatment-emergent AEs will be summarized overall by treatment group and preferred term.

The incidence of common (≥ 2% [after rounding] of participants in any treatment group) TEAEs will be summarized by preferred term and treatment group.

Summary tables will be provided for TEAEs leading to treatment discontinuation and TESAEs if they occurred in 5 or more participants.

9.2.4 SAEs, Deaths and Adverse Events Leading to Study Drug Discontinuation

SAEs, deaths and AEs leading to study drug discontinuation will be tabulated by primary SOC.

9.2.5 Adverse Events of Special Interest

There are no protocol-specified adverse events of special interest for this study.

9.3 Analysis of Laboratory Data

9.3.1 Urine Pregnancy Test

Women of childbearing potential will have urine pregnancy tests performed at the Screening (Day -7) and Day 90/Early Exit visits. At each visit, the investigator should discuss contraceptive use compliance with WOCBP. Positive test results for females of childbearing potential will be listed.

9.3.2 Clinical Laboratory Parameters

Clinical laboratory parameters are not evaluated in this study.

9.4 Analysis of Vital Signs

Vital sign parameters are not evaluated in this study.

9.5 Other Safety Analyses

9.5.1 Biomicroscopy

Biomicroscopy will be performed in each eye at each visit, by slit lamp examination, without pupil dilation, including but not limited to lids/lashes, conjunctiva, cornea and

anterior chamber. Observations for the examination will be graded on a 5-point scale (0=none, 0.5=trace, 1=mild, 2=moderate, 3=severe) except for the anterior chamber (in cells: 0=0 cells, +0.5=1-5 cells, +1=6-15 cells, +2=16-25 cells, +3=26-50 cells, and +4=>50 cells; in flare: 0=None, +1=faint, +2=moderate, +3= marked and +4=intense).

The number and percent of patients with clinically significant biomicroscopy findings at one or more visits will be tabulated. A clinically significant finding is defined as more than one severity grade increase (worsening) from baseline. If a pathology is recorded at a follow-up visit but not at baseline, the baseline will be imputed with the same pathology, with a grade of zero (none).

9.5.2 Currently Corrected Distance Visual Acuity

Currently corrected distance visual acuity will be measured for each eye using the provided distance logarithmic visual acuity chart for testing at 3 meters at visits. The total number of letters read correctly at each visit will be summarized with descriptive statistics by treatment group.

Frequency tables based on the change from baseline in total number of letters read correctly will be provided at each visit for the following categories:

• 3 lines or better than baseline (“Much Better”)

• 2 lines better than baseline (“Better”)

• Between 1 line worse and 1 line better than baseline (“No change”)

• 2 lines worse than baseline e (“Worse”)

• 3 lines or worse than baseline (“Much Worse”)

9.5.3 Best Corrected Distance Visual Acuity

BCVA is measured via subjective refraction for each eye using the provided distance logarithmic visual acuity chart for testing at 3 meters at Screening (Day -7) and Day 90/Early Exit visits. BCVA will be summarized same way described for currently corrected distance visual acuity in Section 9.5.2.

9.5.4 Intraocular Pressure

IOP is measured for each eye using the Goldmann applanation tonometer at each visit. Baseline IOP and change from baseline IOP will be summarized with descriptive statistics by treatment group for participants with glaucoma or ocular hypertension (OHT).

10.0 Other Analyses

10.1.1 Pharmacokinetics/Pharmacodynamics

Pharmacokinetics/pharmacodynamics parameters are not evaluated in this study.

10.1.2 Genetics

Genetics are not evaluated in this study.

11.0 Interim Analyses

No interim analysis is planned for this study.

11.1 Data Monitoring Committee

Data monitoring committee is not required for this study.

12.0 Overall Type-I Error Control

To control the family-wise type I error rate at 0.05 for multiplicity across the hypothesis tests, a hierarchical gatekeeping procedure will be followed.

Step 1: Test the noninferiority hypothesis. If the upper limit of the 2-sided 95% CI is less than 2.3 units, reject H_0 and go to Step 2. Otherwise stop.

Step 2: Test the superiority hypothesis.

13.0 SAP Version History

This SAP is based on the Protocol 2007-301-005 Amendment 2 dated 08 Jun 2020.

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1	07 JAN 2021	Not Applicable	Original version
Amendment 1	02 Aug 2021		Amendment 1

14.0 References

Lemp MA. National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes, CLAO J 1995;21:221-232.

Pflugfelder S. Baylor Fluorescein Corneal Staining Scheme (Unpublished Personal Communication, 2008).

Appendix A. Protocol Deviations

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. The number and percentage of participants with significant protocol deviations that occurred in the randomized treatment period will be summarized by treatment group for ITT population.

Appendix B. Safety Assessments

1. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy (***without*** pupil dilation) will be performed on both eyes at all visits during the study.

The following will be examined at each visit:

- Eyelid/eyelid margins/lashes
- Conjunctiva
- Cornea
- Anterior chamber

Findings other than those listed above will be recorded under "other" for the appropriate location of the finding.

EYELID / EYELID MARGINS / LASHES

Erythema

0	(None)	No erythema
+ 0.5	(Trace)	Localized, minimal (trace) flush reddish color
+ 1	(Mild)	Localized, mild, flush reddish color
+ 2	(Moderate)	Diffuse reddish color encompassing the entire lid margin
+ 3	(Severe)	Deep diffuse reddish color of lid margins and superior and/or inferior eyelid

Edema (eyelids)

0	(None)	No edema
+ 0.5	(Trace)	Localized, minimal (trace) swelling
+ 1	(Mild)	Localized, mild swelling
+ 2	(Moderate)	Diffuse, moderate swelling
+ 3	(Severe)	Diffuse, severe swelling

CONJUNCTIVA (BULBAR AND PALPEBRAL)

Hyperemia

0	(None)	No hyperemia
+ 0.5	(Trace)	Minimal (trace) flush, reddish color
+ 1	(Mild)	Mild flush, reddish color
+ 2	(Moderate)	Bright red color
+ 3	(Severe)	Deep, bright diffuse redness

Edema

0	(None)	No edema
+ 0.5	(Trace)	Localized, minimal (trace) swelling
+ 1	(Mild)	Localized, mild swelling
+ 2	(Moderate)	Diffuse, moderate swelling
+ 3	(Severe)	Diffuse, severe swelling

CORNEA

Edema

0	(None)	No edema
+ 0.5	(Trace)	Localized, minimal (trace) epithelial haze
+ 1	(Mild)	Dull glass appearance of epithelium that may include fine localized microcystic changes
+ 2	(Moderate)	Dull glass appearance of epithelium with large number of cystic changes with or without stromal edema

+ 3	(Severe)	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

ANTERIOR CHAMBER

Cells

0	=	0 cells
+ 0.5	=	1 to 5 cells (trace)
+ 1	=	6 to 15 cells
+ 2	=	16 to 25 cells
+ 3	=	26 to 50 cells
+ 4	=	> 50 cells

Flare

0	=	None: no flare seen
+ 1	=	Faint: faint flare seen
+ 2	=	Moderate: iris and lens details clear
+ 3	=	Marked: iris and lens details hazy
+ 4	=	Intense: fibrin or plastic aqueous

2. Currently Corrected Distance Visual Acuity

At all visits, corrected visual acuity will be measured using a logarithmic visual acuity chart with Sloan letters for testing at 3 meters (9 feet, 10 inches).

Begin by first testing the right eye. Occlude the left eye. The participant should be asked to start on the top line of the bottom right chart (20/50 equivalent). Participants should be told to read the letters from left to right on each line and that the chart has letters only, no numbers. If the participant reads a number, he/she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number.

The participant should be asked to read slowly to achieve best identification of each letter and not to proceed to the next letter until he/she has given a definite answer.

If the participant changes a response (eg, "that was a C not an O") before he/she has read aloud the next letter, then the change must be accepted. If the participant changes a response after having read the next letter, then the change will not be accepted. The examiner must not point to specific letters during the test.

When the letters become difficult to read, or if the participant identifies a letter as one of 2 letters, he/she should be asked to choose one letter and, if necessary, to guess. Participants should be encouraged to continue trying even when letters become difficult to read. Stop testing when 3 or more errors are made on the same line. Use the supplied source document worksheet to mark the letters missed for each line and to enter the number of letters correctly read for each line.

If a participant cannot read the 20/50 equivalent line when instructed, verify that the proper current correction is in place. If the participant is still unable to read the 20/50 equivalent line, have him/her read from the top of the full center chart, letter by letter, and record the number of letters missed and the number of letters correctly read for each line in the source document.

Test the left eye following the same procedures outlined above, except have the participant start on the top line of the bottom left chart (20/50 equivalent). This strategy minimizes letter memorization.

3. BCDVA

Best-corrected visual acuity will be measured at Day -7 (Screening) and Day 90/Early Exit visits using the same logarithmic visual acuity chart with Sloan letters for testing at 3 meters (9 feet, 10 inches) that will be used for the currently corrected distance visual acuity. The LogMar chart will be viewed using a trial frame holding the best-corrected

distance endpoint manifest refraction. (Measuring acuity using the phoropter is acceptable so long as the chart distance is 3 meters.)

Sphere, cylinder, and axis will be determined, and a consistent endpoint should be used, which is generally the least minus sphere that provides the participant's best measured acuity. Visual acuity should be determined using the same procedure used for currently corrected distance visual acuity. The phoropter may be either a plus or minus cylinder design. Values generated should be recorded directly from the phoropter without conversion.

4. IOP (participants with glaucoma or OHT only)

After the Schirmer test with anesthetic is administered, IOP will be measured for each eye at Screening (Day -7) and Baseline (Day 1) and at all scheduled visits for participants with glaucoma or OHT only.

Measurements should be taken using a Goldmann applanation tonometer affixed to a slit-lamp with the participant seated. Additional sodium fluorescein can be applied if needed. Both eyes will be tested, with the right eye preceding the left eye. The measurer looks through the binocular viewer of the slit lamp at low power. The tension knob is preset at low pressure value (4 to 6 mm Hg). The measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the measurer takes his/her fingers off the tension knob and records the IOP reading along with the date and time of day in the source document.

Appendix C. List of Abbreviations

Abbreviation	Definition
AE	adverse event
BCDVA	best-corrected distance visual acuity
CI	confidence interval
DED	dry eye disease
eCRF	electronic case report form
EDS-VAS	Eye Dryness Score - Visual Analog Scale
FWER	family-wise error rate
IES	intercurrent event(s) strategy
IOP	intraocular pressure
ITT	intent-to-treat
IxRS	interactive response system
MD	multidose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
NATF	novel artificial tear formulation
NCI	National Cancer Institute
NEI	National Eye Institute
OD	right eye
OHT	ocular hypertension
OS	left eye
OSDI	Ocular Surface Disease Index® Questionnaire
OTC	over-the-counter
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOC	system organ class
TBUT	tear break-up time
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

Abbreviation	Definition
VAS	visual analog scale
vs	versus
WHO	World Health Organization

Appendix D. Changes to Protocol-planned Analyses

There are no changes from the protocol-planned analyses.

Electronic Signatures

User	Date	Justification
[redacted]	02-Aug-2021 20:44:38 (GMT)	Document Originator Approval
	04-Aug-2021 19:44:44 (GMT)	NC - Study Director Approval
	02-Aug-2021 22:16:07 (GMT)	Subject Matter Expert Approval
	03-Aug-2021 21:36:05 (GMT)	Manager Approval

TITLE PAGE

Protocol 2007-301-005

A Multicenter, Single-masked, Randomized Study to Compare the Efficacy and Safety of a New Artificial Tear Formulation (011516X) with Systane® Ultra Multidose for 90 Days in Participants with Dry Eye Disease

PER-PROTOCOL ANALYSES
DATA EXCLUSION ALGORITHM

Draft: 06-Aug-2021

HISTORY OF CHANGE

Amendment: Not applicable

Date	Description of Change(s)
06-Aug-2021	Initial version (Approved)

1 Introduction

This document is written to detail the algorithms used to define data exclusions from the per-protocol analysis in the 2007-301-005 Amendment 2 and statistical analysis plan (SAP) Amendment 1.0.

The per-protocol (PP) population is defined in SAP section 4.0. The PP analysis will be implemented on the primary efficacy endpoint only. The PP population will consist of participants who contribute data to the PP analysis after implementing the data exclusion algorithms specified in this document. PP population will come from ITT population who are treated. Data from the participants with a protocol deviation that is deemed to affect primary efficacy assessment from a study visit will be excluded from the PP analysis for that study visit.

2 Algorithms to Define Data Exclusion for PP Analysis

2.1. General Rules

Each participant was randomized to receive either 011516X or Systane Ultra Multidose (MD) treatment. Algorithms for data exclusion from PP analysis are defined for primary efficacy analysis of change from baseline in total ocular staining score data of the study eye at Day 90. The algorithm will be applied to all total ocular staining score data of the study eye that are involved in the primary efficacy analysis including that the data from baseline (Day 1), Days 7, 30, 60 and 90/Early Exit.

2.2. Ocular Staining Measurement

Ocular staining measurements are conducted at all study visits for cornea and conjunctiva, and the change from baseline on total staining score at Day 90 is defined as primary efficacy endpoint. Same analysis windows for ITT analysis specified in Statistical Programming Plan will be used in PP analysis.
However, total ocular staining score at Day 90 will use the study visit window of Day 75 to 105 and all ocular staining data collected outside the analysis visit window will either be mapped to earlier visits or be excluded from PP analysis.

2.3. Prohibited Concomitant Medications

Data from the study visits in which ocular staining is potentially affected by prohibited concomitant medications will be considered exclusive for PP analysis. The general rules for total staining data exclusion from PP analysis are provided in protocol deviation requirement specification (PDRS) under code CM-01. The data to be excluded from PP analysis will be stated in the comment field of protocol deviation management tool (PDMT).

2.4. Ocular Concurrent Procedures

Data from the study visits in which ocular staining is potentially affected by ocular concurrent procedures will be considered exclusive for PP analysis. PDRS will provide the category of the PP exclusion under code CP-100. The data to be excluded from PP analysis will be stated in the comment field of PDMT.

2.5. Inclusion Criteria of Baseline Total Ocular Staining Score

Protocol inclusion criteria requires patients to have baseline total staining score of between 6 and 43 with corneal staining score of 5 to 19 and conjunctival staining score of 1 to 24. If a patient's baseline staining score of cornea and conjunctiva in study eye is outside of inclusion criteria, the study eye baseline and all follow up visit total staining score data will be excluded from PP analysis.

2.6. Other Protocol Deviations Impacting Total Staining Measurement

Total staining data will be excluded according to Table 2.6-1 for the following protocol deviations.

Table 2.6-1 Protocol Deviation Impacting Total Staining Score

Protocol Deviation Code/Category	Description	Excluding Period
SI-02: Dosed with wrong study intervention (ICH)	Participant was not dosed with the assigned study intervention label ID	All data during period not dosed with the assigned study intervention label ID will be excluded from the PP analysis.
SI-400: Study Intervention - Reported incorrect dosing for more than 10 days	Participant reported incorrect dosage of study intervention for more than 10 days	All data during incorrect dosing period will be excluded from the PP analysis.
SP-200: Primary efficacy study procedure – not performed per protocol	Corneal and/or Conjunctival Staining was not performed per protocol at Baseline, Days 7, 30, 60 and/or 90 that may impact subject safety or primary efficacy analysis	All total staining score at the procedure date will be excluded from the PP analysis
EC-01: Prior /concurrent clinical study experience	Are currently enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study at the Screening (Day -7) visit	All data will be excluded from the PP analysis.

3 Data Exclusion Reasons and Codes

The reasons and codes for total staining data being excluded from PP analysis is summarized below (Table 3-1).

Table 3-1 Total Staining Data Exclusion Reasons and Codes

Exclusion Reason	Exclusion Code	Affected Analysis Visit and Description
Ocular staining measurement	A100	All affected visits
Prohibited Concomitant Medications	B100	All affected visits
Ocular concurrent procedures	C100	All affected visits
Baseline total staining	D100	Baseline
Protocol Deviation on dosed with wrong study intervention (SI-02)	E100	All affected visits
Protocol Deviation on study intervention – reported incorrect dosing more than 10 days (SI-400)	E101	All affected visits

Protocol Deviation on primary study efficacy procedure – not performed per protocol (SP-200)	E102	All affected visits
Protocol Deviation on prior /concurrent clinical study experience (EC-01)	E-103	All visits