STATISTICAL ANALYSIS PLAN

Study Title:	Randomized, Double-Masked, Parallel Group Study of P-321 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Disease Assessing Safety and Efficacy Over 28 Days
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol P-321-202. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

This is a multi-center, randomized, double-masked, placebo-controlled, parallel group Phase 2b trial designed to evaluate symptoms and signs in subjects with mild to moderate dry eye disease. It is anticipated that approximately 125 subjects with dry eye will need to be screened in order to randomize about 65 subjects and complete approximately 60 subjects. Subjects who meet inclusion/exclusion criteria will be enrolled in a single-masked placebo run-in period for up to 14 days. At the end of the run-in period, eligible subjects will be randomly assigned in a double-masked fashion to receive either 0.017% P-321 Ophthalmic Solution or Placebo TID for 28 days. The study will consist of four study visits and a follow up phone call: Visit 1 (Screening Visit), Visit 2 (Randomization and Treatment Day 1), Visit 3 (Treatment Day 15) and Visit 4 (Day 29, after 28 days of treatment) and a follow up phone call 5-9 days later. Three phone calls to remind subjects of dosing regimen and to inquire about adverse effects will also be done during the study and will occur between Visits 1 and 2, Visits 2 and 3, and Visits 3 and 4. The placebo-run-in is single-masked in that the subjects will remain masked to the treatment during the placebo run-in. However, the treatment is known to the investigator, medical monitor, study site personnel, and those involved in the conduct of the study. The randomized treatment assignments are double-masked in that the treatment will be masked to the investigator, medical monitor, study site personnel, subjects in the study and those involved in the conduct of the study.

This study is designed to evaluate the changes in symptoms and signs of dry eye disease including conjunctival staining of the lid wiper area of the upper eyelid (with photographs if technology is available), corneal staining, bulbar conjunctival staining, and tear break-up-time (TBUT). Dry eye symptom questionnaires including the Symptom Assessment in Dry Eye questionnaire (SANDE), the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, and a 7-item symptom questionnaire will be completed at each visit prior to other assessments. Exploratory assessments of expression of biomarkers of inflammation in the tears and from impression cytology samples collected from the lid wiper and the bulbar conjunctiva will be performed.

Safety will be assessed throughout the study by adverse event monitoring, biomicroscopy and external eye examination, best corrected visual acuity (BCVA), physical examinations, vital signs, clinical laboratory tests, and an assessment of comfort after taking the medication in-clinic.

Eligible subjects will have at least one eye that meets the entry criteria. This will be referred to as the Study Eye. For the purpose of efficacy analysis in this trial, each subject will have only one Study Eye. If a subject has only one qualifying eye, this eye will be the Study Eye. If both eyes of the subject qualify, then the Study Eye will be the eye with the highest total corneal staining score at Visit 1. If the scores for total corneal staining are the same, the Study Eye will be the right eye. The non-Study Eye is referred to as the Fellow Eye.

1.2. SCHEDULE OF VISITS AND PROCEDURES

Event	Visit 1	Phone call	Visit 2	Phone Call	Visit 3	Phone call	Visit 4	ET	Follow up
	Screening Visit Day -14	Day -7 ± 1 to Day 1	Randomization -Treatment Day 1	Day 8 ± 1	Treatment Day 15	Day 22± 1	Day 29	Early Termination Visit	Follow up call 7 days ± 2 after Visit 4
Informed Consent	X								
Eligibility criteria reviewed	X		X						
Medical History/Changes	X		X		X		X	X	X
Concomitant Medication/Changes	X[a]		X		X		X	X	X
Abbreviated Physical Exam	X						X	X	
Vital Signs	X		X		X		X	X	
Urine Pregnancy Test	X						X	X	
Serum Chemistry, Hematology	X				X[b]		X	X	
Dry Eye Symptoms[c]	X		X		X		X		

Event	**Visit 1**	**Phone call**	**Visit 2**	**Phone Call**	**Visit 3**	**Phone call**	**Visit 4**	**ET**	**Follow up**
	Screening Visit Day -14	**Day -7 ± 1 to Day 1**	**Randomization -Treatment Day 1**	**Day 8 ± 1**	**Treatment Day 15**	**Day 22± 1**	**Day 29**	**Early Termination Visit**	**Follow up call 7 days ± 2 after Visit 4**
Study Medication Instillation Technique Training/Observation in Clinic	X[d]		X[e]		X[e]				
Dispense Study Medication	X[d]		X[e]		X[e]				
Drop Instillation Comfort Assessment[f]	X		X		X				
Subject reminder for when to take medication		X		X		X			
Collect Returned Study Medication			X[d]		X[e]		X[e]	X[e]	
Best Corrected Visual Acuity	X		X				X		
Biomicroscopy and External Eye Examination	X		X		X		X	X	
Tear osmolarity & Meibomian gland assessment[g]	X								
Tear Collection for Biomarker[h]			X		X		X		

Event	Visit 1	Phone call	Visit 2	Phone Call	Visit 3	Phone call	Visit 4	ET	Follow up
	Screening Visit Day -14	Day -7 ± 1 to Day 1	Randomization -Treatment Day 1	Day 8 ± 1	Treatment Day 15	Day 22± 1	Day 29	Early Termination Visit	Follow up call 7 days ± 2 after Visit 4
TBUT	X		X		X		X		
Corneal Staining	X		X		X		X		
Bulbar Conjunctival Staining	X		X		X		X		
Lid wiper staining of the upper eyelid[i]	X		X		X		X		
Impression Cytology[j]			X				X		
Schirmer's Test (unanesthetized)	X								
Intraocular Pressure	X								
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X

a. Concomitant medications taken within 28 days of screening will be reviewed
b. Only serum potassium
c. Dry eye symptom questionnaires (SANDE, SPEED, and 7-item symptom questionnaire) will be completed as ordered before any other study assessments are performed at each visit. SANDE Part 1 will be completed at Visits 1-4, and Part 2 will be completed at Visits 2, 3, and 4.
d. Placebo run-in study medication only
e. Double-masked study medication per assigned subject treatment number
f. To be assessed within 5 minutes after dosing in clinic for the Fellow Eye only
g. Meibomian gland assessment to include clinical gland evaluation ± meibography (if available). If available, photographs will become part of the source and electronic data.
h. Must be completed before any ocular staining has occurred. Tears from the Study eye for prostaglandins and from the Fellow Eye for MMP-9 activity
i. Lid wiper staining may include photographs if technology is available. If available, photographs will become part of the source and electronic data.
j. Must be conducted after corneal, conjunctival and lid wiper staining and will be done in the Study Eye only

1.3. GLOSSARY OF ABBREVIATION

AE	Adverse event
ANCOVA	Analysis of Covariance
BCVA	Best corrected visual acuity
CRF	Case report form
IOP	Intraocular pressure
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian gland dysfunction
mITT	Modified Intent-to-Treat
SANDE	Symptom Assessment in Dry Eye questionnaire
SPEED	Standard Patient Evaluation of Eye Dryness questionnaire
TEAE	Treatment emergent adverse event
TBUT	Tear break-up time
WHO	World Health Organization

2. OBJECTIVES

Primary Objective:

The primary objective is to evaluate the efficacy of treatment with 0.017% P-321 taken TID in subjects with mild to moderate dry eye disease after 28 days of treatment on Dry Eye Symptoms.

Secondary Objectives:

The secondary objectives are to evaluate the safety and tolerability of 0.017% P-321 taken TID in subjects with mild to moderate dry eye disease.

Exploratory Objective:
The exploratory objective is to evaluate the expression of biomarkers of inflammation in tears and from impression cytology samples collected from the lid wiper and the bulbar conjunctiva.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

A sample size of approximately 65 randomized subjects is proposed. Assuming a dropout rate prior to Visit 3 of 10%, this provides approximately 60 subjects with post-baseline data. The sample size estimation was based on assumptions about the standard deviation and treatment effect for the change from baseline SANDE global score (Part 2 assessment) from a previous study, protocol P-321-101. At Day 28, the pooled standard deviation for the change from baseline was 22 and the difference in means was 20, representing a standard effect size of 0.9. If the true standard deviation is 22, a sample size of 30 subjects per group will provide at least 90% power to detect a true difference in means of 20 using a two-sided hypothesis test with Type 1 error of 5%. All else being equal, this sample size provides at least 70% power if the treatment difference is at least 15 units or if the standard deviation is no more than 29.

3.2. RANDOMIZATION AND MASKING

For the placebo run-in portion of the screening process, all subjects will receive a placebo vehicle. The placebo-run-in is single-masked in that the subjects will remain masked to treatment during the placebo run-in. However, the treatment is known to the investigator, medical monitor, study site personnel, and those involved in the conduct of the study.

Following the placebo-run-in period, approximately 65 subjects will be randomly assigned in a 1:1 allocation ratio to either 0.017% P-321 Ophthalmic Solution or placebo, stratified by clinical site. The randomized treatment assignments are double-masked in that the treatment will be masked to the investigator, medical monitor, study site personnel, subjects in the study and those involved in the conduct of the study.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

All analyses of the primary and secondary efficacy endpoints will include site as a fixed effect in the statistical models. If the endpoint is a change from baseline endpoint, the baseline value will also be included as a covariate in the statistical model.

3.3.2. Examination of Subject Subsets

There are no planned subset analyses.

3.3.3. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple testing.

3.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects. See section 3.3.5 for details of imputing missing dates. A sensitivity analysis will be performed for the primary endpoint imputing missing data by multiple imputation. See section 5.2.1 for details. Unless otherwise specified, other missing data will not be imputed.

3.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation, all events with an incomplete end date are assumed to have ended on or before the day the form was completed. In an effort to minimize bias, the project statistician will impute dates in a systematic, but reasonable manner. For missing dates during the placebo run-in phase, if the month/year is the same as the Day -14 month/year then the date will be set to the date of Day -14. In other cases, missing days will be imputed as the day component of Day -14; missing months/years will be imputed as the month/year of Day -14. For missing dates during the double-masked phase, if the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

3.3.6. Presentations by Study Visit

When data are collected serially over time, individual data presentations may include by-visit displays. For these presentations, visits will be presented according to the nominal visit as obtained from the CRF or laboratory data. If assessments are collected with multiple dates or times within a given visit, the result closest to the scheduled visit date will be used for summary presentations. If two measurements have the same distance to the expected date, the earlier value will be used. If a subject has multiple non-missing values on the same date, then the last one is used, as determined by the time collected, if available.

3.3.7. Definitions and Terminology

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to administration of the first dose of double-masked study drug.

Day 1
Day 1 is the day/time that the double-masked study drug is first initiated.

Study Day
Study Day is defined relative to Day 1.
For events occurring prior to Day 1, the study day is calculated as:
Study Day = event date – date of Day 1.

For events occurring after Day 1, the study day is calculated as:

Study Day = event date – date of Day 1 + 1.

Study Visit
Study Visit is the nominal visit as recorded on the CRF.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Adverse Event (AE)
An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product; which does not necessarily have a causal relationship with this treatment. All adverse events will be recorded on the Adverse Event CRF.

Treatment-emergent Adverse Event (TEAE) for Placebo Run-in Period
During the placebo run-in period, a treatment-emergent AE (TEAE) is an AE that either commenced following initiation of the placebo run-in period study treatment or was present prior to study treatment but increased in frequency or severity following initiation of study treatment.

Additionally, it is assumed that an AE which was reported to have started on Day -14 (start of placebo run-in period) without an associated onset time occurred after the initiation of study treatment and is therefore a treatment-emergent adverse event (TEAE).

Treatment-emergent Adverse Event for Double-masked Period
During the double-masked period, a treatment-emergent AE is an AE that either commenced following initiation of the double-masked period study treatment or was present prior to study treatment but increased in frequency or severity following initiation of double-masked study treatment. Additionally, it is assumed that an AE which was reported to have started on Day 1 (start of double-masked period) without an associated onset time occurred after the initiation of study treatment and is therefore a treatment-emergent adverse event. AEs reported without an onset date are also assumed to be TEAEs.

Treatment-related Adverse Event
A Treatment-related AE is any adverse event reported on the CRF that is marked as being Related or Possibly Related to the study medication. Additionally, it is assumed that an AE without a relationship is a Treatment-related AE.

Concomitant Medications for Placebo Run-in Period
Concomitant medications for the placebo run-in period are those medications taken during the placebo run-in period.

Concomitant Medications for Double-Masked Period
Concomitant medications for the double-masked period are those medications taken while on the double-masked period study treatment.

Previous Medications for Placebo Run-in Period
Previous medications for the placebo run-in period are those medications that ended prior to the initiation of the placebo run-in period study treatment.

Previous Medications for Double-Masked Period
Previous medications for the double-masked period are those medications that ended prior to the initiation of the double-masked period study treatment.

Study Eye
If a subject has only one qualifying eye, that eye will be the Study Eye. If both eyes of the subject qualify, then the Study Eye will be the eye with the highest total corneal staining score. If the scores for total corneal staining are the same, the Study Eye will be the right eye.

3.4. TIMING OF ANALYSES

A final analysis will be conducted once the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked. This analysis may exclude the biomarker data. The analysis of the biomarker data will be conducted once the final biomarker data are available.

4. ANALYSIS POPULATIONS

The populations for analysis will include the modified Intent-to-Treat Population (mITT), Safety Population, and Run-in Population.

4.1. MODIFIED INTENT-TO-TREAT (MITT) POPULATION

The modified Intent-to-Treat Population (mITT) will include all randomized subjects who have at least a baseline and one post-baseline SANDE part 1 assessment. This is the primary population for efficacy analyses and subjects will be analyzed based on their randomized treatment.

4.2. SAFETY POPULATION

The Safety Population will include all subjects who receive at least one dose of double-masked study medication in either eye. All safety analyses for the double-masked portion of the study will be conducted on the Safety Population, analyzed as treated.

4.3. RUN-IN POPULATION

The Run-in Population will include all subjects who receive at least one dose of single-masked placebo in either eye during the run-in period. Safety analyses for the single-masked portion of the study will be conducted on the Run-in Population.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

The term 'treatment group' refers to all subjects on the same dosing regimen. There will be 2 treatment groups in this study: 0.017% P-321 Ophthalmic Solution and placebo.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05 unless otherwise stated.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject disposition will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation at any point also will be presented by treatment group. Additionally, the number of weeks on study and study drug will be summarized for all treated subjects.

Demographic data and baseline characteristics including age, gender, race, ethnicity, and weight will be summarized by treatment group and overall using descriptive statistics.

Ocular and non-ocular medical history will be descriptively summarized, and dry eye and other ocular history including MGD, BCVA, IOP, symptoms upon entry, corneal and conjunctival staining, staining in the lid wiper region, TBUT, tear osmolarity, and Schirmer tests will be summarized by treatment group and overall using descriptive statistics. This information will be statistically compared between the two randomized treatment groups using a 2-sided Wilcoxon rank-sum test for continuous variables, a 2-sided Chi-Square Test for nominal categorical variables, or a van Elteren test for ordinal categorical variables with more than 2 levels.

5.2. EFFICACY ANALYSIS

Analyses of efficacy will be conducted using the Study Eye. For all efficacy analyses by Study Eye, a secondary analysis will be conducted using all qualifying eyes. The primary and secondary efficacy analyses will be performed on the mITT Population and presented by treatment group. The dry eye symptom questionnaires can be viewed in Appendix IV of the protocol.

5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline to Day 29 (Visit 4) in the SANDE questionnaire global symptom score from Part 1. The primary efficacy comparison will be the mean change from baseline in the SANDE global symptom score for the 0.017% treatment arm compared to placebo.

5.2.2. Primary Efficacy Analysis

The SANDE Questionnaire Part 1 is comprised of two 100mm VAS scales. One measures frequency of symptoms from rarely (0) to all the time (100). The other measures severity of symptoms from very mild (0) to very severe (100). The global score is calculated as the square root of the product of the two measurements.

The SANDE Part 1 global symptom score and change from baseline will be summarized by treatment and study visit. The change from baseline at Day 29 will be assessed for differences between the 0.017% P-321 treatment group and placebo using a mixed model repeated measures analysis with fixed effects for treatment, study site, visit, and treatment by visit interaction, with the baseline value as a covariate. The following 3 covariance structures will be considered: AR(1), CS, and UN. The covariance structure with the lowest AIC will be selected. The corresponding 95% confidence interval for the difference will be presented. A secondary analysis will be performed assessing the change from baseline at Day 15 from the same mixed model repeated measures analysis.

The descriptive statistics for change from screening to baseline will be presented by treatment.

Additionally, the proportion of subjects with improvement from baseline, no change from baseline, and worsening from baseline to Day 29 will be summarized by treatment group and overall. The analysis will also be performed for Day 15.

A sensitivity analysis will be performed where missing data will be imputed using the method of multiple imputation. Multiple imputation relies on the assumption that the data are missing at random. This method of imputation produces unbiased estimators of the mean and standard error, and, as such, is preferred over single imputation methods (Dziura et al., 2013). For this method, the procedure requires production of multiple datasets containing plausible values for each missing value. Using a set of values rather than a single value better accounts for the uncertainty about the value being imputed. SAS PROC MI will be used to generate 10 possible imputed datasets. The analysis described in the previous paragraph will be performed ten times, once for each dataset. The results from the analysis from each of the 10 datasets will be combined using SAS PROC MIANALYZE to produce a single inferential result.

Mean and 95% CI for SANDE Part 1 global symptom scores will be plotted by treatment and study visit.

5.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are as follows:

1. Change from baseline to Day 15 and Day 29 in the SPEED questionnaire total symptom score.
2. Changes from baseline to Day 15 and Day 29 in each of the 7-item symptom questionnaire scores.
3. Change from baseline to Day 15 and Day 29 in staining of the Lid Wiper area.
4. Change from baseline to Day 15 and Day 29 in bulbar conjunctival staining total score.
5. Change from baseline to Day 15 and Day 29 in corneal staining total score.
6. Changes from baseline to Day 15 and Day 29 in tear breakup time (TBUT).
7. Change in symptom frequency score and severity score as recorded by the subject using the SANDE Part 2 assessment.
8. Change from baseline to Day 15 and Day 29 in the SANDE symptom frequency and

severity scores from Part 1.

9. The proportion of subjects with at least a 20% improvement from baseline to Day 15 and Day 29 in the SANDE global symptom score from Part 1 (and in the frequency and severity scores).
10. The proportion of subjects with at least a 10% improvement over 14 days from Day 1 to Day 15 and from Day 15 to Day 29 in symptom frequency score and severity score using the SANDE Part 2 assessment.

5.2.4. Secondary Efficacy Analyses

1. The SPEED questionnaire total symptom score is calculated by summing responses from the frequency of symptoms (0-3 scale) and severity of symptoms (0-4 scale) sections. There are 5 symptoms, so the total score can range from 0 to 35. The change from baseline to Day 29 in the SPEED questionnaire total symptom score will be analyzed in a similar manner as the primary endpoint. A secondary analysis will be performed assessing the change from baseline at Day 15.

   Additionally, the proportion of subjects with improvement from baseline, no change from baseline, and worsening from baseline to Day 29 will be summarized by treatment group and overall. The analysis will be repeated at Day 15.

   The descriptive statistics for change from screening to baseline will be presented.

   The type of symptoms and when they occur from question 1 on the SPEED questionnaire will be summarized by treatment at Day 15 and Day 29.

   Mean and 95% CI for SPEED questionnaire total symptom scores will be plotted by treatment and study visit.

2. The 7-item questionnaire comprises 100mm VAS scales for 7 symptoms: Eye dryness, Burning/Stinging, Photophobia, Foreign Body Sensation, Blurred Vision, Itching, and Pain. The scales range from no discomfort (0) to maximal discomfort (100). Changes from baseline to Day 29 in each of the 7 measurements will be analyzed individually in a similar manner as the primary endpoint. A secondary analysis will be performed assessing the change from baseline at Day 15.

   Additionally, the proportion of subjects with improvement from baseline, no change from baseline, and worsening from baseline to Day 29 will be summarized by treatment group and overall. The analysis will be repeated at Day 15.

   The descriptive statistics for change from screening to baseline will be presented by treatment.

Mean measurements and 95% CI for these questionnaires will be plotted by treatment and study visit separately for all 7 items.

3. Lid wiper staining is measured using a horizontal length of staining score (0-3) and a sagittal height of staining score (0-3). The individual scores for these two dimensions are averaged to calculate a final Fluorescein staining score and Lissamine Green staining score. The staining score of the lid wiper area is defined as the maximum of the Fluorescein and Lissamine scores. Thus, possible values for the staining score of the lid wiper area are: 0, 0.5, 1, 1.5, 2, 2.5, and 3. The primary analysis for the change from baseline to Day 29 will utilize the Study Eye and will be analyzed in a similar manner as the primary endpoint. An additional analysis will be conducted using scores from all qualifying eyes. For this analysis, the change from baseline at Day 29 will be assessed using a mixed model repeated measures analysis with fixed effects for treatment, study site, visit, eye, and treatment by visit interaction with the baseline value as a covariate and a random effect for subject. The following 3 covariance structures will be considered: AR(1), CS, and UN. The covariance structure with the lowest AIC will be selected. A secondary analysis will be performed assessing the change from baseline at Day 15 from the same mixed model.

   The descriptive statistics for change from screening to baseline will be presented by treatment.

   The analysis will be repeated for Fluorescein scores and Lissamine scores independently.

   Mean and 95% CI for staining scores of the lid wiper area will be plotted by treatment and study visit.

4. Bulbar conjunctival staining total score is defined as the sum of scores from 6 regions: Temporal, Temporal Superior, Temporal Inferior, Nasal Superior, Nasal Inferior, and Nasal. The score for each region ranges from 0 to 3. Thus, the bulbar conjunctival staining total score can range from 0 to 18. The change from baseline to Day 29 will be analyzed in a similar manner as the Change from baseline to Day 29 in staining of the Lid Wiper area. A secondary analysis will be performed assessing the change from baseline at Day 15.

   The descriptive statistics for change from screening to baseline will be presented by treatment.

   The analysis will be repeated for the inferior nasal region (region 5) individually.

   Mean and 95% CI for bulbar conjunctival staining total scores will be plotted by treatment and study visit.

5. Corneal staining total score is defined as the sum of scores from 5 regions: Central, Superior, Temporal, Nasal, and Inferior. The score for each region ranges from 0 to 3. Thus, the corneal staining total score can range from 0 to 15. The change from baseline to Day 29 will be analyzed in a similar manner as the Change from baseline to Day 29 in staining of the Lid Wiper area. A secondary analysis will be performed assessing the change from baseline at Day 15.

The descriptive statistics for change from screening to baseline will be presented by treatment.

The analysis will be repeated for the inferior region (region 5) individually.

Mean and 95% CI for corneal staining total scores will be plotted by treatment and study visit.

6. The change from baseline to Day 29 in TBUT (seconds) will be analyzed in a similar manner as the Change from baseline to Day 29 in staining of the Lid Wiper area. A secondary analysis will be performed assessing the change from baseline at Day 15.

   The descriptive statistics for change from screening to baseline will be presented by treatment.

   Mean and 95% CI of TBUT will be plotted by treatment and study visit.

7. The SANDE Part 2 is comprised of two 100mm VAS scales. One measures the frequency of symptoms at the current visit as compared to the frequency of symptoms at the previous visit. The score ranges from much less frequent (-50) to much more frequent (50). The second VAS measures the severity of symptoms at the current visit as compared to the severity of symptoms at the previous visit. The score ranges from much less severe (-50) to much more severe (50).

   The change from previous visit for frequency and severity of symptoms will be summarized individually by treatment at Day 1, Day 15, and Day 29. Differences between the 0.017% P-321 treatment group and placebo will be assessed using a mixed model repeated measures analysis with fixed effects for treatment and study site, visit, and visit by treatment interaction. The following 3 covariance structures will be considered: AR(1), CS, and UN. The covariance structure with the lowest AIC will be selected.

   Additionally, the proportion of subjects with improvement from previous visit, no change from previous visit, and worsening from previous visit at Day 1, Day 15, and Day 29 will be summarized by treatment group and overall.

8. The SANDE Part 1 is comprised of two 100mm VAS scales. One measures frequency of symptoms from rarely (0) to all the time (100). The other measures severity of symptoms from very mild (0) to very severe (100). The change from baseline to Day 29 in the SANDE symptom frequency and severity scores from Part 1 will be analyzed individually in a similar manner as the primary endpoint. A secondary analysis will be performed assessing the change from baseline at Day 15.

   Additionally, the proportion of subjects with improvement from baseline, no change from baseline, and worsening from baseline to Day 29 will be summarized by treatment group and overall. The analysis will be repeated at Day 15

9. Subjects whose SANDE global symptom score from Part 1 decreases by 20% or more from baseline to Day 29 will be considered responders. Subjects whose scores do not decrease by 20% or more will be considered non-responders. Differences between the proportion of responders between the 0.017% P-321 treatment group and placebo will be assessed using a logistic regression model with fixed effects for treatment, study site, and baseline value. The odds ratio and corresponding 95% confidence interval will be presented. The analysis will also be performed for the frequency and severity scores individually. A secondary analysis will be performed assessing the change from baseline at Day 15.

   A Sensitivity analysis will be performed where all subjects with missing data will be considered non-responders.

10. A 10% or more improvement from previous visit will be defined as a SANDE Part 2 value of 5 or more. Subjects whose scores show an improvement of symptoms by 10% or more from baseline to Day 15 will be considered responders at Day 15. Subjects whose scores show an improvement of symptoms by 10% or more from Day 15 to Day 29 will be considered responders at Day 29. Differences between the proportion of responders between the 0.017% P-321 treatment group and placebo will be assessed separately at Day 15 and at Day 29 using a logistic regression model with fixed effects for treatment and study site.

5.2.5. Exploratory Endpoints

1. Change from baseline to Day 29 in expression of the COX-2, Cytokeratin 10, HLA-DR, IFN-γ, IL-1β, and IL-8 genes in the lid wiper.
2. Change from baseline to Day 29 in expression of the COX-2, Cytokeratin 10, HLA-DR, IFN-γ, IL-1β, and IL-8 genes in the bulbar conjunctiva.
3. Change from baseline to Day 29 in MMP-9 Activity in tears.
4. Change from baseline to Day 29 in Prostaglandin levels (PGE_2, PGD_2, PGF_{2x}, TxB_2, and PGI_2) in tears.
5. Pearson correlations between the response of 7-item questionnaire symptoms, corneal staining, conjunctival staining, lid wiper staining, TBUT, and biomarkers with baseline scores for tear osmolarity, Meibomian gland assessment, and the Schirmer test.

5.2.6. Exploratory Analyses

The expression of each gene and change from baseline in the lid wiper will be summarized separately by treatment and study visit. For each of the 6 genes, the change from baseline at Day 29 will be assessed for differences between the 0.017% P-321 treatment group and placebo using an ANCOVA model with fixed effects for treatment, study site, and baseline value.

The expression of the same 6 genes in the bulbar conjunctiva, MMP-9 activity levels, and prostaglandin levels will be analyzed in a similar manner. A secondary analysis will be performed assessing the change from baseline at Day 15 for MMP-9 and Prostaglandins.

The Pearson correlations between the change from baseline to Day 29 in corneal stain score with the baseline scores for tear osmolarity, Meibomian gland assessment, and the Schirmer test and their corresponding p-values will be presented by treatment group and overall.

The analysis will be repeated for each symptom from the 7-item, SANDE and SPEED questionnaires, corneal staining, conjunctival staining, lid wiper staining, TBUT, and biomarkers.

5.3. SAFETY

Safety analyses will be run separately on Safety population and the Run-in population.

5.3.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 preferred term and system organ classification. If a subject experiences multiple events that map to a single preferred term, the greatest severity grade and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication. Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA system organ class and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by strongest relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized. Separate summaries will be performed for those AEs occurring during the placebo run-in period.

All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. AEs will be flagged by run-in or double-masked treatment period as appropriate.

Any adverse event with a missing onset date will be considered to be a TEAE occurring during the double-masked treatment period.

5.3.2. Clinical Laboratory Assessments

Clinical laboratory assessments will be performed at Visits 1 and 4 (or Early Termination Visit). Actual values and changes from baseline for clinical laboratory test results will be summarized by study visit and treatment using descriptive statistics. Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges.

5.3.3. Concomitant Medications

Previous and concomitant medications will be coded using the World Health Organization (WHO) dictionary version September 2016. Concomitant medications for the placebo run-in period and for the double-masked period will both be summarized by frequency of drug classification and generic drug name by treatment and overall. Previous and concomitant medications will be presented in a data listing.

5.3.4. Other Safety Analyses

Actual values and changes from baseline for BCVA and vital signs will be summarized by treatment and study visit using descriptive statistics. A separate table will be produced for the Run-in Population summarizing screening, Day 1, and Change from Screening to Day 1 values.

Biomicroscopy and eye examination data will be summarized separately for each eye by treatment and study visit with descriptive statistics for each area. Areas include lashes, eyelid (erythema), eyelid (edema), conjunctive (erythema), conjunctiva (edema), tear film debris, cornea (endothelial changes), cornea (edema), anterior chamber (cells), anterior chamber (flare), and lens pathology. Shifts from baseline will be presented for each eye, OD and OS.

Drop instillation discomfort will be summarized by treatment and study visit with descriptive statistics.

6. PROTOCOL DEVIATIONS

Possible protocol deviations will be identified by the clinical team. These data will be displayed in a data listing and sorted by treatment group and subject.

7. CHANGES IN THE PLANNED ANALYSES

No deviations in the conduct of the study or the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

8. REFERENCES

Dziura JD, Post LA, Zhao Q, Fu Z, Peduzzi P. Strategies for dealing with Missing data in clinical trials: From Design to Analysis. Yale Journal of Biology and Medicine 2013; 86:343-358.

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).

- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.

- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.

- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.

- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.

    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.

    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.

- Sorting: Listings will be sorted by treatment group, subject number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.

- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.

- The presentation of numerical values will adhere to the following guidelines:
  - ♦ Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - ♦ Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - ♦ Means will be reported to the same number of significant digits as the parameter.
  - ♦ Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

10. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

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14.1.1	Subject Disposition (All Subjects Enrolled)
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14.1.2.2	Dry Eye Assessments at Screening (All Subjects Enrolled)
14.1.3	Study Drug Exposure (All Subjects Treated)
14.1.4.1	Concomitant Medications for Double-Masked Period by Generic Name and Drug Classification (Safety Population)
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Efficacy (all analyses on mITT population)

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14.2.2.2	Summary of SPEED Questionnaire Type of Symptom Experience and When Symptoms Occur
14.2.3.1.1	Summary of 7-item Symptom Questionnaire Score – Eye Dryness
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14.2.4.1.1	Summary of Staining of the Lid Wiper Area – Study Eye
14.2.4.2	Summary of Staining of the Lid Wiper Area – All Qualifying Eyes
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14.2.5.1.1	Summary of Bulbar Conjunctival Staining Total Score – Study Eye
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14.2.5.3	Summary of Bulbar Conjunctival Inferior Nasal Region Score – Study Eye
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14.2.6.1.1	Summary of Corneal Staining Total Score – Study Eye
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14.2.8.2	Summary of SANDE Part 2 Symptom Severity Score

14.2.9.1	Summary of SANDE Questionnaire Part 1 Symptom Frequency Score
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14.3.1.1.1	Summary of Treatment-emergent Adverse Events – Double Masked Period (Safety Population)
14.3.1.1.2	Summary of Treatment-emergent Adverse Events – Placebo Run-in Period (Run-in Population)
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14.3.1.3.1	Adverse Events Related to Study Drug by System Organ Classification and Preferred Term – Double Masked Period (Safety Population)
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14.3.1.4.1	Treatment-emergent Serious Adverse Events by System Organ Classification and Preferred Term - Double Masked Period (Safety Population)
14.3.1.4.2	Treatment-emergent Serious Adverse Events by System Organ Classification and Preferred Term – Placebo Run-in Period (Run-in Population)
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14.3.6.1	Summary of Vital Signs by Study Visit (Safety Population)
14.3.6.2	Summary of Vital Signs by Study Visit (Run-in Population)
14.3.7.x.1	Summary of Biomicroscopy and Eye Examination Data (Safety Population)
14.3.7.x.2	Summary of Biomicroscopy and Eye Examination Data (Safety Population) • Lashes • Eyelid Erythema • Eyelid Edema • Conjunctival Erythema • Conjunctival Edema • Tear Film Debris • Corneal Endothelial Changes • Corneal Edema • Anterior Chamber Cells • Anterior Chamber Flare • Lens pathology
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16.2.6.3.2 Expression of the COX-2, Cytokeratins, HLA-DR, IFN-γ, IL-1β, IL-8 Genes in the Lid Wiper
16.2.6.3.3 Expression of the COX-2, Cytokeratins, HLA-DR, IFN-γ, IL-1β, IL-8 Genes in the Bulbar Conjunctiva
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14.2.4.1.2	Summary of Staining of the Lid Wiper Area – Study Eye
14.2.5.1.2	Summary of Bulbar Conjunctival Staining Total Score – Study Eye
14.2.6.1.2	Summary of Corneal Staining Total Score – Study Eye
14.2.7.1.2	Summary of Tear Breakup Time (TBUT) – Study Eye