STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked, Randomized, Active-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Preservative-Free Formulation with Lumify® 0.025% in Adult Subjects with Ocular Redness

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Protocol Number: # 908

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Date: 16JAN2023

Version: 1.0

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SAP Date: **16JAN2023**

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Signing Time: 16-Jan-2023 | 19:18 EST
19E2CD45068042C9A1B0796BEC84BCE4

16-Jan-2023 | 19:18 EST

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2A777B73090F4723971C0CEA248F8C1D

16-Jan-2023 | 21:51 EST

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Signing Time: 17-Jan-2023 | 09:20 PST
69BDEA79DDC34561845956733DFFEC70

17-Jan-2023 | 09:20 PST

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List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BTOS-PF	Birmonidine Tartate Ophthalmic Solution, Preservative-free Formulation
CI	Confidence Interval
CRO	Clinical Research Organization
CS	Clinically Significant
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
OU	*Oculus uterque* (Both Eyes)
PDF	Portable Document Format
PPP	Primary Per-Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SPP	Secondary Per-Protocol
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
WHO Drug	World Health Organization Drug Dictionary
WOCF	Worst Observation Carried Forward

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol 908, Version 2.0 dated 27OCT2021.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E9 (R1) Guideline entitled Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principals for Clinical Trials, and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

The primary objective is to demonstrate that the efficacy of brimonidine tartrate ophthalmic solution preservative-free formulation (BTOS-PF) 0.025% is non-inferior to Lumify® 0.025% for treating ocular redness in a population of adult subjects.

The secondary objective is to compare the safety of BTOS-PF 0.025% with Lumify® 0.025%.

2.1 Primary Endpoint

The primary efficacy endpoint is

- Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1.

2.2 Secondary Endpoints

Secondary efficacy endpoints will be evaluated hierarchically, as follows:

1. Change from pre-instillation ocular redness score evaluated by the investigator at 1 (+0.5) minute after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1
2. Change from pre-instillation ocular redness score evaluated by the investigator (0-4 unit scale, allowing half unit increments) at:
    i. 1 minute after investigational drug instillation at Visit 2
    ii. 5 minutes after investigational drug instillation at Visit 2
    iii. 1 minute after investigational drug instillation at Visit 3
    iv. 5 minutes after investigational drug instillation at Visit 3

3. Change from pre-instillation ocular redness score evaluated by the investigator at 360 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1
4. Change from pre-instillation ocular redness score evaluated by the investigator at 480 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1.
5. Ocular redness score evaluated by the subject as captured in subjects' redness grading diary throughout the treatment period (0-4 unit scale, NOT allowing half unit increments).

2.3 Exploratory Endpoint

The supportive efficacy endpoint is:

- Total clearance of ocular redness assessed by the investigator at each post-instillation time point at each visit.

2.4 Safety Variables

The following safety variables will be recorded:

- Adverse Events (AEs; reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) at Distance
- Slit Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Ocular Rebound defined as:
    - Increase of at least 1 unit in mean ocular redness score evaluated by the investigator at Visit 4 (0-4 unit scale, allowing half unit increments) compared to pre-instillation score at Visit 1, or
    - Increase of at least 1 unit in mean ocular redness score evaluated by the subject as captured in subject's redness diary in the follow-up period after dosing has ceased (0-4 unit scale, NOT allowing half unit increments) compared to diary day 1 (pre-dose morning assessment)
- Vital Signs (resting blood pressure and pulse)
- Physical Examination
- Dilated ophthalmoscopy

2.5 Tolerability Variables

- Drop comfort assessment (0-10 unit scale) assessed upon instillation, at 30 seconds, and at 1 minute post instillation at Visit 1
- Drop comfort descriptor questionnaire assessed at 3 minutes post-instillation at Visit 1

2.6 Statistical Hypotheses

At each of eight post-instillation times at Visit 1, the null hypothesis (H_0) is that the difference between the mean redness scores for the Test (μ_T) and Control (μ_c) formulations is 0.22 points or greater. The alternative hypothesis (H_1) is that the difference is less than 0.22 points.

$$H_0: \mu_T - \mu_c \geq 0.22$$
$$H_1: \mu_T - \mu_c < 0.22$$

The non-inferiority margin is the absolute value of one half of the smallest (in absolute value) upper confidence limit around the difference in redness scores (test minus control) observed over eight post-instillation times (5 to 240 minutes) during each of two placebo controlled randomized clinical trials (B&L studies 11-100-0015 and 861).

The hypotheses above will be tested for each of the eight post-instillation times at Visit 1 utilizing two-sided 95% confidence intervals (CIs) around the difference between means (BTOS-PF 0.025% minus Lumify® 0.025%) constructed as for two-sample t-tests. If the upper confidence limit does not exceed 0.22 units at any of the eight time points, then the study will be considered a success, and BTOS-PF 0.025% will be considered statistically non-inferior to Lumify® 0.025% for investigator-rated ocular redness.

By requiring that the null hypotheses must be rejected at all eight post-instillation times to demonstrate success for the primary efficacy endpoint, the familywise type I error rate for the primary efficacy hypothesis tests is bounded above by the significance level of each hypothesis test (two-sided α = 0.05).

Statistical inference will be performed for the secondary efficacy endpoints only if the primary efficacy endpoints demonstrate non-inferiority and statistical inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order from the list of endpoints in Section 2.2.

2.7 Estimands

The primary comparisons in this trial will be between brimonidine tartrate ophthalmic solution preservative-free formulation (BTOS-PF) 0.025% versus Lumify® 0.025% at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1 for the Intent-to-Treat (ITT) population using the following estimands.

- Population: subjects with ocular redness defined through enrollment criteria
- Endpoint:
  - Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation at Visit 1.
- Intercurrent event:
  - Non-optimal compliance is ignored. [treatment policy strategy]
  - Missing data due to withdrawal due to lack of efficacy or AEs (assumed to be missing not at random [MNAR]) will be imputed employing single imputation using worst observation carried forward (WOCF) [hypothetical strategy].

- Ocular redness scores on or after the use of prohibited medication will be set to missing (assumed to be MNAR) for the remainder of the study and will be imputed using single imputation of last observation carried forward (LOCF) [hypothetical strategy].
- Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs (assumed to be missing at random [MAR]): will be imputed employing randomized treatment-based Fully Conditional Specification (FCS) regression methodology [hypothetical strategy].
-

- Population-level summary:
  - Difference in the mean ocular redness at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation at Visit 1 between BTOS-PF 0.025% and Lumify® 0.025%.

3. Study Design and Procedures

3.1 General Study Design

This is a multi-center, double-masked, randomized, active-controlled, parallel-group, efficacy and safety study that will enroll approximately 386 subjects at up to six clinical sites. Subjects with ocular redness will be randomized to receive either brimonidine tartrate ophthalmic solution 0.025%, preservative-free formulation, or Lumify® (brimonidine tartrate ophthalmic solution 0.025%). Subjects will be treated with study drug for approximately 4 weeks.

Five visits will take place during this study: Screening Visit (Day -28 to 1), Visit 1 (Baseline; Day 1), Visit 2 (Day 15 ± 2 days), Visit 3 (Day 29 + 2 days), and Visit 4 (Study Exit; Day 36 + 1 day). Efficacy assessments will be performed at Visits 1, 2, and 3. Tolerability assessments will be performed at Visit 1. Safety assessments will be performed at selected visits.

Efficacy assessments include ocular redness evaluated by the investigator in-office and ocular redness evaluated by the subject as captured in subject's redness diary. Tolerability assessments include drop comfort assessment and drop comfort descriptor questionnaire, both evaluated by the subject. Safety assessments include AEs, vital signs, BCVA, IOP, dilated ophthalmoscopy, slit lamp biomicroscopy, and ocular rebound.

Study visits will be referred to in all tables and listings by the scheduled visit name. **Error! Reference source not found.** shows the scheduled study visits, their planned study day and the acceptable visit window for each study visit:

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in **Table** 1.

Table 1 Schedule of Assessments:

PROCEDURE/ASSESSMENTS	Screening[1]	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4
	Day -28 to Day 1	Day 1	Day 15 ± 2	Day 29 + 2	Day 36 + 1
Informed consent/HIPAA[2]	X				
Demographics	X				
Medical History	X				
Concomitant Medications	X	X	X	X	X
Urine Pregnancy Test (for females of childbearing potential)[3]		X		X	X
Physical Examination[4]		X		X	
Vital Signs[5]		X	X	X	
BCVA at Distance		X	X	X	X
Slit lamp biomicroscopy[6]		X	X	X	X
Intraocular Pressure (IOP)		X		X	
Dilated Ophthalmoscopy		X		X	
Randomization		X			
In-Office Redness Assessment		X[7]	X[8]	X[8]	X
In-Office Investigational Drug Instillation		X[9]	X[10]	X[10]	
Drop Comfort/Descriptor Assessment[11]		X			
Dispense Investigational Drug and Dosing Diary[10]		X	X		
Collect Investigational Drug and Dosing Diary[10]			X	X	
Dispense Redness Grading Diary				X	
Collect Redness Grading Diary					X
Assessment of adverse events	X	X	X	X	X
Exit					X

[1] If there is no washout period, the Screening Visit and Visit 1 can occur on the same day.
[2] Informed consent must be signed before any study-related procedure can be performed. If washout of a medication is necessary, informed consent must be obtained prior to Visit 1.

[3] Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[4] Physical examination includes general health, head, eyes, ears, nose, throat (HEENT), and any other comments.
[5] Vital signs (resting blood pressure and pulse) with body weight will be collected at Visits 1 and 3 and without body weight at Visit 2.
[6] Evaluated prior to and post investigational drug instillation at Visits 1, 2, and 3.
[7] Investigator will evaluate ocular redness prior to investigational drug instillation and at 1 (+0.5), 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), 240(+15), 360(+15), and 480(+15) minutes post investigational drug instillation.
[8] Investigator will evaluate ocular redness prior to investigational drug instillation and approximately 1 and 5 minutes post-instillation.
[9] Performed by the subject or subject's caregiver while under the observation of the unmasked designee.
[10] Performed by the unmasked designee.
[11] Subjects will assess comfort upon instillation, at 30 seconds, and at 1 minute post-instillation using 0-10 unit scale for each eye at Visit 1. Subjects also will select comfort descriptor terms from a predetermined list at 3 minutes post-instillation at Visit 1.
[12] Complete urine pregnancy test if Visit-3 is early termination visit

4. Study Treatments

- Investigational Product: Brimonidine tartrate ophthalmic solution 0.025% preservative-free formulation
- Comparator Product: Lumify® (brimonidine tartrate ophthalmic solution 0.025%)

4.1 Method of Assigning Subjects to Treatment Groups

At Visit 1, approximately 386 subjects will be randomly assigned at a ratio of 1:1 to the following treatments:

- Brimonidine tartrate ophthalmic solution 0.025%, preservative-free formulation (BTOS-PF) (N = 193)
- Lumify® (brimonidine tartrate ophthalmic solution 0.025%) (N= 193)

Each subject who signs an informed consent form will be assigned a unique subject number in the Interactive Web Response System (IWRS). Once a subject meets all qualification criteria at Visit 1, they will be randomized to brimonidine tartrate ophthalmic solution 0.025%, preservative free formulation or Lumify® (brimonidine tartrate ophthalmic solution) 0.025% in a 1:1 ratio. Subject numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted. Subject numbers will be created (in the following format, 3-digit site number plus 3-digit subject number) in the IWRS. Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across the treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

4.2 Masking and Unmasking

Subjects will be assigned to treatments based on a randomization schedule. The investigator, site staff, subject, clinical research organization (CRO), and Sponsor personnel involved in the monitoring or conduct of the study will be masked to the treatment assignments. The randomization list will be produced prior to study enrollment by a statistician not otherwise involved in the trial.

5. Sample Size and Power Considerations

A sample size of 183 subjects per treatment group will have approximately 90% power to demonstrate non-inferiority of BTOS-PF 0.025% to Lumify® 0.025% at all eight post-instillation times at Visit 1 using a two-sample t-test and assuming a non-inferiority limit of 0.22 units, mean difference of 0 units, and a common standard deviation of 0.50 units with one-sided alpha of 0.025. Assuming a 5% dropout rate, 193 subjects will be randomized to each treatment group (386 total subjects).

5.1 Justification of Non-Inferiority Margin

The non-inferiority margin is the absolute value of one half of the smallest (in absolute value) upper confidence limit around the difference in redness scores (test minus control) observed over eight post-instillation times (5 to 240 minutes) during each of two placebo-controlled randomized clinical trials (B&L studies 11-100-0015 and 861).

6. Data Preparation

6.1 Input Data

Study data will primarily be recorded on the electronic Case Report Forms (eCRFs) supplied by Statistics & Data Corporation (SDC) using iMednet Electronic Data Capture (EDC) system.

When all prerequisites for database lock have been met, including availability of all masked external data, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of all final versions of external vendor data, with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

6.2 Output Data

Data from EDC and external data will be transferred to Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM Version 1.4 model and will be implemented using the SDTM Implementation Guide Version 3.3 and the SDTM Controlled Terminology Version 2022-09-30. ADaM data will follow the ADaM Version 2.1 model and will be implemented using the ADaM Implementation Guide Version 1.1. Both SDTM and ADaM will be validated using Pinnacle 21 Version 4.0.1. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML Version 2.0 model.

7. Analysis Populations

7.1 Intent-to-Treat

The Intent-to-Treat (ITT) population includes all randomized subjects. Subjects will be analyzed according to the treatment to which they were randomized.

7.2 Primary Per Protocol

The Primary Per-Protocol population (PPP) will include subjects in the ITT who do not have significant protocol deviations likely to affect the primary endpoint analysis. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PPP population will be analyzed as treated.

7.3 Secondary Per-Protocol

The Secondary Per-Protocol (SPP) population will include subjects in the ITT who do not have significant protocol deviations likely to affect the secondary endpoints and analyses. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the SPP population will be analyzed as treated.

7.4 Safety

The Safety population includes all randomized subjects who received at least 1 dose of study drug. All subjects in the Safety population will be analyzed according to the treatment they received. All safety analyses will be based on the Safety population.

8. General Statistical Considerations

8.1 Units of Analysis

For efficacy, tolerability, and non-ocular safety analyses, the unit of analysis will be the subject. In the cases where assessments are recorded for each eye, the average of the eyes will be used. Adverse events will also be summarized at the subject level; if an AE occurs in either or both eyes, the subject will be counted as having the AE.

8.2 Missing or Inconclusive Data Handling

In general, there will be no imputation of missing data other than as described in Section 2.7 and for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.

- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

8.3 Definition of Baseline

For Ocular redness, baseline is defined as the last measurement prior to the first dose instillation at each visit.

8.4 Data Analysis Conventions

All data analysis will be performed by SDC. Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and

percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between test treatment and control will be calculated as BTOS-PF 0.025% minus Lumify® 0.025 and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be sorted by subject treatment, , visit/time point (as applicable), and parameter as applicable.

8.5 Adjustments for Multiplicity

The Type I error rate for the primary efficacy analysis will be controlled by requiring the primary efficacy hypotheses test results to be statistically significant for all eight time points at Visit 1 (5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes post-instillation) to declare success for the primary endpoint. The overall Type I error rate including the primary and secondary efficacy analyses will be controlled by a hierarchical testing structure. Specifically, statistical inference for the secondary efficacy analyses will only be performed if the primary analyses are successful, after which inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order of the secondary endpoints from Section 13.2.

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study by visit and overall, and discontinued from the study. Disposition will be summarized by treatment group and overall for all randomized subjects.

The number of subjects in ITT, PPP, SPP, and Safety analysis populations will be displayed by treatment group and overall. Percentages of number of subjects will be calculated using randomized subjects as the denominator.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group and overall for all randomized subjects. The reasons for study discontinuation that will be summarized include: AE, lost to follow-up, death, pregnant, lack of efficacy, study terminated by sponsor, voluntary withdrawal, and other. Treatment related discontinuations will also be displayed. A subject listing will be provided which includes the date and reason for premature study discontinuation in addition to the informed consent date and protocol version for which informed consent was signed.

The number and percentage of subjects with any, major, and minor protocol deviations will be summarized by treatment group and overall for all randomized subjects. Protocol deviations will be classified as major

or minor prior to the closure of the database during a masked review of each protocol deviation. Major deviation or protocol violation is defined to have occurred when there is non-adherence to the protocol that results in a significant, additional risk to the subject; when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria), and the subject was enrolled without prior sponsor approval; or when there is non-adherence to FDA regulations and/or ICH GCP guideline.

Important protocol deviations leading to exclusion from the Primary and Secondary Per-Protocol Population will include, but not limited to the following.

1. Ineligibility
2. Use of any prohibited medication potentially affecting the primary or secondary endpoints

Exclusion from Primary or Secondary Per-Protocol Population will be reviewed prior to the closure of the database during a masked review of the data.

The number of subjects with major protocol deviations along with deviation categories will be summarized by treatment group and overall, in a table. A subject listing will be provided which includes the date of the deviation, the deviation description, the action taken for the deviation, the classification of whether the deviation was judged to be major or minor, whether the deviation was COVID-19 related or not, and if the deviation excludes the subject from the Primary Per-Protocol and/or Secondary Per-Protocol analysis populations.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected in this study include date of birth, age, sex, childbearing potential, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Iris color will be summarized at the subject level with a category for heterochromia if a subject records a different eye color for each eye. Demographic variables will be summarized for the ITT and Safety populations, separately.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years.

A subject listing that includes all demographic variables will be provided.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the ITT Population. Ocular medical history will be similarly summarized at the subject level. If a subject reports the

same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs and PTs within an SOC will be ordered by descending frequency based on all subjects.

Listings of medical history will be generated separately for ocular and non-ocular data.

11.2 Concomitant Medications and Procedures

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO Drug) Global, B3, March 2022 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than one medication per ATC class. At each level of subject summarization, a subject will be counted once if they report one or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC classes and preferred names within an ATC class will be ordered by descending frequency based on all subjects.

Listings of concomitant medications and procedures will be generated.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Subjects will be provided with a dosing diary to document QID dosing. Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

$$\text{Compliance (\%)} = \frac{\text{Number of Actual Doses Received} \times 100\%}{\text{Number of Expected Doses}}$$

The number of actual doses received will be calculated by counting the number of dosed records in the subject diary and the in-office instillation CRF pages. From Visit 1 to Visit 3, subjects are expected to be dosed 4 times day, including in-office doses. However, on Visit 1, they get only 1 dose on-site and are

instructed to take no further doses at home. The at-home dosing starts on the day after Visit 1. The expected number of doses will be calculated as:

For subjects who complete Visit 3

$$4 \times [(\text{Date of Visit 3} - \text{Date of First Dose})] + 1$$

For subjects who discontinue without completing Visit 3

$$4 \times [(\text{Date of Study Last Dose from the Dosing Diary Page} - \text{Date of First Dose})] + 1$$

Subjects that discontinue without completing Visit 3 will be expected to take 4 doses on their last dose date. A categorical dosing compliance variable will also be derived as non-compliant (< 80%), compliant (≥ 80% and ≤ 125%), and over compliant (> 125%).

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the ITT population. The compliance category defined above will be summarized with discrete summary statistics.

A subject listing of dosing compliance will also be produced.

12.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

For subjects that complete Visit 3,

$$\text{Extent of Exposure (days)} = (\text{Date of Visit 3} - \text{Date of First Dose}) + 1$$

For subjects don't complete Visit 3

$$\text{Extent of Exposure (days)} = (\text{Date of Last Dose} - \text{Date of First Dose}) + 1$$

Extent of treatment exposure for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group using the safety population. A subject listing of study drug instillation will also be produced.

13. Efficacy Analyses

All assessment data for efficacy analyses will be provided in subject listings.

13.1 Primary Analysis

The primary efficacy endpoint is

- Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5 (+1), 15 (+1), 30 (+1), 60 (+10), 90 (+10), 120 (+15), 180 (+15), and 240 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1.

Summary statistics will be shown for the pre-dose ocular redness score and for each of the post-dose time points. BTOS-PF 0.025% will be compared to Lumify® 0.025% for the primary efficacy parameter of ocular redness as evaluated by the investigator (post-instillation assessments) for each of the eight time points at Visit 1 using two-sided 95% CIs around the difference between means (BTOS-PF30 0.025% minus Lumify® 0.025%) constructed as for two-sample t-tests with a non-inferiority limit of 0.22 units. Missing data and intercurrent events for the primary endpoint will be treated as described in Section 2.7.

Data will be transposed to horizontal structure before passing to PROC MI.

```
PROC MI DATA=INDATA SEED=697471 NIMPUTE=30 OUT=OUT1 MINIMUM=0 MAXIMUM=4
ROUND=0.5;
Class trt01pn;
VAR BASE POST_5min POST_15min POST_30min POST_60min POST_90min POST_120min
POST_180min POST_240min;
FCS REG (/details);
RUN;
```

where

- `INDATA` is the name of the input dataset
- `Trt01pn is the planned treatment`
- `OUT1` is the name of the output dataset
- `BASE` is the baseline assessment
- `POST_5min` is the assessment at 5 mins post dose
- `POST_15min` is the assessment at 15 mins post dose
- `POST_30min` is the assessment at 30 mins post dose
- `POST_60min` is the assessment at 60 mins post dose
- `POST_90min` is the assessment at 90 mins post dose
- `POST_120min` is the assessment at 120 mins post dose
- `POST_180min` is the assessment at 180 mins post dose
- `POST_240min` is the assessment at 240 mins post dose

The following SAS® code will then be used execute the t-test for each imputed dataset:

```
PROC SORT DATA=OUT1; BY ATPTN _IMPUTATION_; RUN;
```

where

- `OUT1` is the name of the input dataset

- ATPTN is the analysis time point
- _IMPUTATION_ is the imputation number

and

```
ods output statistics=ttest (where=(method in ('', "Pooled")));
proc ttest data=out1 sides=2 alpha=0.05;
      by atptn _imputation_;
      class TRTPN;
      var aval;
   run;
```

where

- OUT1 is the name of the input dataset
- _IMPUTATION_ is the imputation number
- TRTPN is the planned treatment
- aval is the redness score

The estimates and standard errors across imputations will be combined using the following code

```
PROC MIANALYZE DATA=ttest;
MODELEFFECTS mean;
STDERR;
ODS OUTPUT PARAMETERESTIMATES=PEST;
RUN;
```

13.1.1 SENSITIVITY ANALYSIS

The following sensitivity analysis will be done on the primary endpoint

- SP1: Repeat the primary efficacy analysis on the ITT population with observed data only. No single or multiple imputations will be performed.
- SP2: Repeat the primary efficacy analysis on the ITT population where all the missing redness scores and redness scores on or after prohibited medication use are imputed using the worst (highest) ocular redness score. No multiple imputations will be performed.
- SP3: Repeat the primary efficacy analysis on the ITT population where all the missing redness scores and redness scores on or after prohibited medication use in the BTOS-PF arm are imputed using the worst (highest) ocular redness score and the Lumify arm are imputed using the best (lowest) ocular redness scores. No multiple imputations will be performed.
- SP4: Repeat the primary efficacy analysis on the PPP population with observed data only. No single or multiple imputations will be performed.
- SP5: Repeat the primary efficacy analysis on the PPP using the same imputation strategy as primary efficacy endpoint.

- SP6: Repeat the primary efficacy analysis on the ITT population where all the missing values and redness scores on or after prohibited medication use are imputed using a regression based multiple imputation strategy. No single imputations will be performed.
- SP7: Repeat the primary efficacy analysis on the ITT population where all the missing values and redness scores on or after prohibited medication use are imputed using multiple imputations with MNAR assumption by searching for the tipping point. The tipping point is the shift value causing the final test result to be reversed from non-inferior to inferior. The tipping point analysis will be done at each of the primary efficacy timepoints – (5, 15 30, 60, 90 120, 180 and 240 minutes post-instillation). The shift value, mean difference with SE, and 95%CI will be presented. The shift range and size will be determined when executing the analysis. The following SAS code will be used.

```
proc mi data=indata seed=987414 nimpute=30 out=out1;
class trt01pn;
fcs reg (/details);
mnar adjust (/shift=xx adjustobs=(trt='BTOS-PF')); /** shift value will be
entered here. **/
var base post_5min post_15min post_30min post_60min post_90min post_120min
post_180min post_240min;
run;

ods output statistics=ttest (where=(method in ('', "pooled")));
proc ttest data=out1 sides=2 alpha=0.05;
by atptn _imputation_;
class trtpn;
var aval;
run;

proc mianalyze data=ttest;
modeleffects mean;
stderr;
ods output parameterestimates=pest;
run;
```

13.2 Secondary Analyses

Secondary efficacy endpoints will be evaluated hierarchically, as follows:

1. Change from pre-instillation ocular redness score evaluated by the investigator at 1 (+0.5) minute after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1
2. Change from pre-instillation ocular redness score evaluated by the investigator (0-4 unit scale, allowing half unit increments) at:
    i. 1 minute after investigational drug instillation at Visit 2

ii. 5 minutes after investigational drug instillation at Visit 2
iii. 1 minute after investigational drug instillation at Visit 3
iv. 5 minutes after investigational drug instillation at Visit 3

3. Change from pre-instillation ocular redness score evaluated by the investigator at 360 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1
4. Change from pre-instillation ocular redness score evaluated by the investigator at 480 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1
5. Ocular redness score evaluated by the subject as captured in subjects' redness grading diary throughout the treatment period (0-4 unit scale, NOT allowing half unit increments)

Secondary efficacy endpoints 1 thorough 4 will be analyzed using the same estimand as the primary efficacy endpoint on the ITT population. Secondary endpoint 5, which is redness grading diary data will be analyzed as described in Section 13.2.2.

The change from pre-instillation in investigator-rated redness will be compared between treatment groups utilizing the same methods as in the primary efficacy analyses [i.e. two sided 95% confidence intervals around the difference between group means (BTOS-PF 0.025% minus Lumify® 0.025%) constructed as for two-sample t-tests for each post-instillation time point at each visit]. BTOS-PF.025% will be considered statistically non-inferior to Lumify® 0.025% for the change from pre-instillation in investigator-rated redness at a given time and visit if the upper confidence limit does not exceed 0.22 units.

13.2.1 Sensitivity Analysis for Secondary Endpoints

The following sensitivity analyses will be performed for secondary endpoints 1 through 5.

SS1: Repeat the secondary efficacy (endpoints 1 through 5) analyses on the SPP population using the same imputation strategy as the primary efficacy endpoint.

SS2: Repeat the secondary efficacy (endpoints 1 through 5) analyses on the ITT population where the redness scores after intercurrent events (including missing redness scores and redness scores during prohibited medication use) are not imputed.

SS3: Repeat the secondary efficacy (endpoints 1 through 5) analyses on the SPP population where the redness scores after intercurrent events (including missing redness scores and redness scores during prohibited medication use) are not imputed.

13.2.2 Redness Diary Data Analysis

Ocular redness as recorded in the subject diaries from Visit 1 to Visit 2 and Visit 2 to Visit 3 post-instillation will be analyzed using a generalized linear model accounting for repeated measures. The model will contain treatment, day, and treatment by day interaction using a compound symmetry variance-covariance structure. If the model fails to converge, other variance-covariance structures will be used. Daily post-instillation averages for each date recorded in subject diaries will be used for each subject. The daily

average will be computed and used if there is at least one score is provided per day. If there are no redness scores recorded on a day, the average will not be computed and daily average be left missing. Redness scores from start of prohibited medications until end of study will not be used and set to missing. All the missing data will be imputed implicitly by the repeated measures mixed model.

If the upper limit of the 95% confidence around the LS mean difference (BTOS-PF 0.025% minus Lumify® 0.025%) is less than 0.19 unit, BTOS-PF 0.025% will be declared statistically non-inferior to Lumify® 0.025% for the subject-rated ocular redness assessment.

The repeated measures analysis will be done in SAS as below

```
proc mixed data=afinal nobound;
by avisit;
class usubjid day trtpn;
model aval =  day trtpn / alpha=0.05 solution ddfm=kenwardroger;
repeated / subject = usubjid v vcorr type=un;
lsmeans trtpn  / pdiff cl alpha=0.05
run;
```

where

- aval is the daily average redness score
- day is the scheduled study day
- avisit is the visit range Visit 1- Visit 2, Visit 2 – Visit 3

13.3 Exploratory Efficacy Analysis

The supportive efficacy endpoint is:

- Total clearance of ocular redness assessed by the investigator at each post-instillation time point at each visit

Subjects with total clearance of ocular redness (redness score of 0 based on investigator assessment) will be summarized using counts and percentages by treatment group for each post-instillation time point at each visit. Treatment comparisons will be made separately for each time point using Pearson's chi-squared test or Fisher's exact test if any of the expected cell counts are less than five. This analysis will be done on the ITT population.

```
proc freq data=indata;
by avisit atpt;
table trtpn*critfl/chisq fisher;
run;
```

where

- avisit is the visit

- atpt is the timepoint
- critfl is criteria flag for subjects with total clearance at that visit. Y for subjects with total clearance and N otherwise.
- trtpn is the planned treatment

13.4 Subgroup Analysis

Ocular redness at Visit 1 using observed data only will be repeated for the following subgroups.

- Age Category (<65, >=65)
- Gender
- Race
- Ethnicity
- Iris Pigmentation
- Site

Summary statistics, 95%CI for the mean, mean difference, associated 95% CI, and p-value from a two-sample t-test between BTOS-PF and Lumify will be produced, Inferential statistics will be produced only if both the arms have at least 2 subjects in that subgroup.

14. Safety Analyses

All safety analyses will be conducted using the Safety population.. The safety of BTOSPF 0.025% compared to Lumify® 0.025% will be assessed by the review of all of the safety parameters.

14.1 Adverse Events

An AE is any untoward medical occurrence in a subject participating in a clinical study, which does not necessarily have a causal relationship with the study product/procedure. The AE reporting period ends upon study exit. Study drug includes the investigational drug under evaluation and control given during any stage of the study. All AEs will be coded using the MedDRA Version 25.0.

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study drug, or that worsened following administration of study drug. Adverse events recorded in the eCRF which are not treatment-emergent will not be included in the summary tables but will be included in the AE data listings.

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to them by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Awareness of a sign or symptom but is easily tolerated, requires no treatment, and does not interfere with subject's daily activities.
- *Moderate:* Low level of concern to the subject and may interfere with daily activities but can be relieved by simple therapeutic care.

- *Severe*: Interrupts the subject's daily activities and requires systemic therapy or other treatment.

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- *Related*: There is at least a reasonable possibility that the AE/Serious Adverse Event (SAE) is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE..
- *Not Related*: There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists..

Only related TEAEs are considered as treatment-related TEAEs.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least TEAE, by treatment group and overall . This summary will also include breakdowns of TEAEs further categorized as ocular or non-ocular, treatment-related TEAEs, treatment-emergent serious adverse events (TE-SAEs), TEAEs leading to early study treatment discontinuation, TEAEs by maximum severity for both ocular and non-ocular TEAEs, and TEAEs leading to death.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE of each type, along with the number of such AEs observed, by treatment group. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level by treatment group. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOCs will be listed in descending frequency of BTOS-PF; PTs will be listed in order of descending frequency for BTOS-PF within each SOC.

Separate summaries will be provided for the following categories of TEAEs:

- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- Ocular Treatment-emergent SAEs (TE-SAEs)
- Non-ocular TE-SAEs
- Non-serious TEAEs occurring in at least 1%, 2%, 3%, 4%, and 5% of subjects in either treatment group. (five summaries)

Summaries of TEAEs by maximum severity will be presented for ocular TEAEs and non-ocular TEAEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and

PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximum severity.

The following tables will be repeated for the subgroups mentioned in Section 13.4 (Age category, Gender, Race, Ethnicity, Iris Pigmentation).

1. Overall Summary of AEs
2. Summary of Ocular AEs by SOC and PT
3. Summary of Non-Ocular AEs by SOC and PT

All AEs will be presented in a subject listing. The AEs leading to study treatment discontinuation will be listed separately. In addition, all SAEs will be presented in a separate listing.

14.2 Best Corrected Visual Acuity at Distance

The logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed at Visits 1, 2, 3, and 4 using an Early Treatment Diabetic Retinography Study (ETDRS) chart. Subjects should use their most recent correction to attain their BCVA.

The observed and change from baseline BCVA will be summarized for each eye using continuous descriptive statistics by visit for each treatment group. A subject listing of visual acuity will also be produced.

14.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the lid and lid margin: erythema, swelling; Conjunctiva: erythema/hyperemia, chemosis; cornea: edema, erosion, endothelial condition, lens pathology; and anterior chamber: cells, flare will be performed at each visit, and evaluated prior to and post investigational drug instillation at Visits 1, 2, and 3.

Table 3 provides the slit-lamp biomicroscopy region and the corresponding grading scale for the results.

Table 3. Slit Lamp Biomicroscopy Regions and Grading Scales

Region	Grading Scale
Cornea: Erosion	0 (None) +1 (Mild) +2 (Moderate) +3 (Severe)
Cornea: Edema	0 (None) +0.5 (Mild) +1 (Moderate) +2 (Severe), +3 (Very Severe)
Lid and Lid Margin: Swelling Conjunctiva: Chemosis Cornea: Endothelial Condition, Lens Pathology Anterior Chamber: Cells, Flare	0 (None) +1 (Mild) +2 (Moderate) 3 (Severe) +4 (Very Severe)
Conjunctiva: Erythema/Hyperemia Lid and Lid Margin: Erythema	0 (None) +0.5 +1 (Mild) +1.5 +2 (Moderate) +2.5 +3 (Severe) +3.5 +4 (Very Severe).

The results will be summarized using counts and percentages for each treatment group at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses. A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

Summary statistics including change from pre-instillation at Visit 1, 2 and 3 will also be produced.

14.4 Intraocular Pressure

Subjects' IOP will be assessed by non-contact tonometry in each eye at Visits 1 and 3. Results will be taken from a single measurement and will be recorded in mmHg.

The IOP values and changes from baseline for each eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group. A subject listing of IOP will also be produced.

14.5 Ocular Rebound

Ocular Rebound defined as:

1. Increase of at least 1 unit in mean ocular redness score evaluated by the Investigator at Visit 4 (0-4 unit scale, allowing half unit increments) compared to pre-instillation score at Visit 1.

   OR

2. Increase of at least 1 unit in mean ocular redness score evaluated by the subject as captured in subject's redness diary in the follow-up period, after dosing has ceased (0-4 unit scale, NOT allowing half unit increments) compared to diary day 1 (predose morning assessment). The mean ocular redness scores during the follow-up period is computed by taking the mean of the daily averages (as described in Section 13.2.2) from Visit 3 to Visit 4. This average score from Visit 3 to Visit 4 will be compared against the first available dairy score to calculate change.

The percentage of subjects meeting the investigator assessment (criteria 1) and subject assessment (criteria 2) will be summarized separately for each treatment group. A subject listing of ocular rebound will also be produced.

14.6 Physical Examination

The physical examination parameters for Head, Eye, Ear, Nose, and Throat; and General Health will be graded as normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS) and summarized by treatment group using counts and percentages at Visits 1 and 3 (including a summary of baseline values). A subject listing of the physical examination results will also be produced.

14.7 Vital Signs

Vital signs, including systolic, diastolic BP, pulse, and weightwill be summarized with continuous descriptive statistics at Visits 1, 2, and 3 by treatment group. Change from Visit 1 will also be summarized at Visits 2 and 3.

A subject listing of the vital signs results will also be produced.

14.8 Dilated Ophthalmoscopy

Dilated Ophthalmoscopy parameters – Choroid, Eye, Vitreous Chamber, Macula, Optic Nerve and Retina , will be graded as normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS). These results will be summarized by treatment group at Visits 1 and 3 on the Safety Population. A subject listing of dilated ophthalmoscopy results will also be produced.

15. Tolerability Analysis

15.1 Drop Comfort Assessment

At Visit 1, drop comfort will be assessed, on a 0-10 scale where 0 is very comfortable and 10 is very uncomfortable, upon instillation, at 30 seconds post instillation, and 1 minute post instillation for both eyes. Drop comfort assessment scores will be summarized with continuous descriptive statistics at Visit 1 by treatment group. The scores will be averaged over both eyes and summarized.

A subject listing of drop comfort assessment results will also be produced.

15.2 Drop Comfort Questionnaire

At Visit 1, 3 minutes post-instillation, the subject will be asked three questions assessing drop comfort using the response words Burning, Comfortable, Cool, Filmy, Gentle, Gritty, Irritating, Refreshing, Smooth, Soothing, Sticky, and Stinging. Subjects can also provide their own word response with an "Other" category. The counts and percentage of subjects in each of these response word categories will be summarized by treatment group. The results of those questions also will be presented in the same listing as for drop comfort assessment.

16. Changes from Protocol-Stated Analyses

The following changes from the protocol are noted

- Change in the definition of the ITT population. The definition in the protocol includes subjects who received at least one dose of study drug. This has been modified to include all randomized subjects.
- The intercurrent event of use of prohibited medications is not mentioned in the protocol. The SAP includes analysis methods for handling this intercurrent event.
- Additional sensitivity analyses not mentioned in the protocol have been added.
- The protocol mentions that missing primary endpoint data at any time point of Visit 1 will be removed from the primary per-protocol population. however, the primary estimand imputations will handle these missing values.
- The protocol states that Ocular TEAEs will be summarized by relationship to study drug. Instead, treatment-related ocular TEAEs will be summarized.
- The non-inferiority limit for the secondary endpoint of redness diary has been updated to from 1 to 0.19.

17. References

BL908 Study Protocol Version 2.0 Dated 27OCT2021

18. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

19. Tables

Tables that will be included in the topline delivery are shown in boldface font.

Table Number	Title	Population
Table 14.1.1.1	**Subject Disposition**	**All Screened Subjects**
Table 14.1.2	Major Protocol Deviations	Intent-to-Treat Population
Table 14.1.3.1	**Demographics**	**Intent-to-Treat Population**
Table 14.1.3.2	Demographics	Safety Population

Table 14.1.4.1	Ocular Medical History	Intent-to-Treat Population
Table 14.1.4.2	Non-Ocular Medical History	Intent-to-Treat Population
Table 14.1.5.1	Ocular Concomitant Medications	Intent-to-Treat Population
Table 14.1.5.2	Non-Ocular Concomitant Medications	Intent-to-Treat Population
Table 14.1.5.3	**Treatment Compliance**	**Safety Population**
Table 14.1.5.4	**Treatment Exposure to Study Drug**	**Safety Population**
Table 14.2.1.1	**Ocular Redness at Visit 1 - Multiple Imputations with Primary Estimand**	**Intent-to-Treat Population**
Table 14.2.1.2	**Ocular Redness at Visit 1 - Observed Data Only**	**Intent-to-Treat Population**
Table 14.2.1.3	Ocular Redness at Visit 1 - WOCF Imputation	Intent-to-Treat Population
Table 14.2.1.4	Ocular Redness at Visit 1 - WBOCF Imputation	Intent-to-Treat Population
Table 14.2.1.5	Ocular Redness at Visit 1 - Observed Data Only	Primary Per-Protocol Population
Table 14.2.1.6	Ocular Redness at Visit 1 - Multiple Imputations with Primary Estimand	Primary Per-Protocol Population
Table 14.2.1.7	Ocular Redness at Visit 1 - Multiple Imputations with MAR Assumption	Intent-to-Treat Population
Table 14.2.1.8	Ocular Redness at Visit 1 – Tipping Point Analysis	Intent-to-Treat Population
Table 14.2.2.1.1	**Ocular Redness at Secondary Time Points – Multiple Imputations with Primary Estimand**	**Intent-to-Treat Population**
Table 14.2.2.1.2	Ocular Redness at Secondary Time Points – Multiple Imputations with Primary Estimand	Secondary Per-Protocol Population
Table 14.2.2.1.3	**Ocular Redness at Secondary Time Points – Observed Data Only**	**Intent-to-Treat Population**
Table 14.2.2.1.4	Ocular Redness at Secondary Time Points - Observed Data Only	Secondary Per-Protocol Population
Table 14.2.2.2.1	**Ocular Redness Diary Grading - MMRM Analysis**	**Intent-to-Treat Population**
Table 14.2.2.2.2	Ocular Redness Diary Grading - MMRM Analysis	Secondary Per-Protocol Population
Table 14.2.2.3.1	Ocular Redness by Visit - Observed Data Only	Intent-to-Treat Population
Table 14.2.2.3.2	Ocular Redness by Visit and Age - Observed Data Only	Intent-to-Treat Population
Table 14.2.2.3.3	Ocular Redness by Visit and Sex - Observed Data Only	Intent-to-Treat Population
Table 14.2.2.3.4	Ocular Redness by Visit and Race - Observed Data Only	Intent-to-Treat Population
Table 14.2.2.3.5	Ocular Redness by Visit and Ethnicity - Observed Data Only	Intent-to-Treat Population

Table 14.2.2.3.6	Ocular Redness by Visit and Iris Color - Observed Data Only	Intent-to-Treat Population
Table 14.2.2.3.7	Ocular Redness by Visit and Site - Observed Data Only	Intent-to-Treat Population
Table 14.2.2.4.1	Ocular Redness Diary Grading – Observed Data Only	Intent-to-Treat Population
Table 14.2.2.4.2	Ocular Redness Diary Grading by Age – Observed Data Only	Intent-to-Treat Population
Table 14.2.2.4.3	Ocular Redness Diary Grading by Sex – Observed Data Only	Intent-to-Treat Population
Table 14.2.2.4.4	Ocular Redness Diary Grading by Race – Observed Data Only	Intent-to-Treat Population
Table 14.2.2.4.5	Ocular Redness Diary Grading by Ethnicity – Observed Data Only	Intent-to-Treat Population
Table 14.2.2.4.6	Ocular Redness Diary Grading by Iris Color – Observed Data Only	Intent-to-Treat Population
Table 14.2.2.5.1	**Total Clearance of Ocular Redness by Time Point and Visit**	**Intent-to-Treat Population**
Table 14.2.2.5.2	Total Clearance of Ocular Redness by Time Point and Visit and Age	Intent-to-Treat Population
Table 14.2.2.5.3	Total Clearance of Ocular Redness by Time Point and Visit and Sex	Intent-to-Treat Population
Table 14.2.2.5.4	Total Clearance of Ocular Redness by Time Point and Visit and Race	Intent-to-Treat Population
Table 14.2.2.5.5	Total Clearance of Ocular Redness by Time Point and Visit and Ethnicity	Intent-to-Treat Population
Table 14.2.2.5.6	Total Clearance of Ocular Redness by Time Point and Visit and Iris Color	Intent-to-Treat Population
Table 14.3.1.1.1	**Overall Summary of Treatment-Emergent Adverse Events**	**Safety Population**
Table 14.3.1.1.2	Overall Summary of Treatment-Emergent Adverse Events by Age	Safety Population
Table 14.3.1.1.3	Overall Summary of Treatment-Emergent Adverse Events by Sex	Safety Population
Table 14.3.1.1.4	Overall Summary of Treatment-Emergent Adverse Events by Race	Safety Population
Table 14.3.1.1.5	Overall Summary of Treatment-Emergent Adverse Events by Ethnicity	Safety Population
Table 14.3.1.1.6	Overall Summary of Treatment-Emergent Adverse Events by Iris Pigmentation	Safety Population
Table 14.3.1.2.1	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.2.2	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age	Safety Population
Table 14.3.1.2.3	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Sex	Safety Population

Table 14.3.1.2.4	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Race	Safety Population
Table 14.3.1.2.5	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Ethinicity	Safety Population
Table 14.3.1.2.6	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Iris Pigmentation	Safety Population
Table 14.3.1.2.7	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in at Least 1% of Subjects	Safety Population
Table 14.3.1.2.8	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in at Least 2% of Subjects	Safety Population
Table 14.3.1.2.9	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in at Least 3% of Subjects	Safety Population
Table 14.3.1.2.10	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in at Least 4% of Subjects	Safety Population
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Table 14.3.1.3	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
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Table 14.3.2.1	Best Corrected Visual Acuity (logMAR)	Safety Population
Table 14.3.2.2.1	Slit Lamp Biomicroscopy - Qualitative Summary	Safety Population
Table 14.3.2.2.2	Slit Lamp Biomicroscopy - Quantitative Summary	Safety Population
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Table 14.3.3.2	Drop Comfort Questionnaire	Safety Population
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20. Listings

Listing Number	Listing Name	Population
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Listing 16.2.1	Subject Disposition	All Randomized Subjects
Listing 16.2.2	Protocol Deviations	All Randomized Subjects
Listing 16.2.3.1	Analysis Populations	All Randomized Subjects
Listing 16.2.3.2	Inclusion Exclusion Criteria	All Randomized Subjects
Listing 16.2.4.1	Demographics	All Randomized Subjects
Listing 16.2.4.2	Ocular Medical History	All Randomized Subjects
Listing 16.2.4.4	Prior and Concomitant Medications	All Randomized Subjects
Listing 16.2.4.5	Concomitant Procedures	All Randomized Subjects
Listing 16.2.5.1	Study Drug Instillation - Diary	All Randomized Subjects
Listing 16.2.5.2	In-Office Study Drug Instillation	All Randomized Subjects
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Listing 16.2.6.1	Ocular Redness In-Office Assessment	All Randomized Subjects
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Listing 16.2.7.1	All Adverse Events	All Randomized Subjects
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Listing 16.2.8.4	Dilated Ophthalmoscopy	All Randomized Subjects
Listing 16.2.8.5	Physical Examination	All Randomized Subjects
Listing 16.2.8.6	Vital Signs	All Randomized Subjects
Listing 16.2.8.7	Urine Pregnancy Test Results - Female Subjects Only	All Randomized Subjects
Listing 16.2.9	In-Office Study Drug Instillation Comfort Score and Questionnaire	All Randomized Subjects

Listing Number	Title	Population
Listing 16.1.7	Randomization Schedule	All Randomized Subjects
Listing 16.2.1	Subject Disposition	

Listing 16.2.3.1	Analysis Populations	All Randomized Subjects
Listing 16.2.3.2	Inclusion Exclusion Criteria	All Randomized Subjects
Listing 16.2.4.1	Demographics	All Randomized Subjects
Listing 16.2.4.2	Ocular Medical History	All Randomized Subjects
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Listing 16.2.5.2	In-Office Study Drug Instillation	All Randomized Subjects
Listing 16.2.6.1	Ocular Redness In-Office Assessment	All Randomized Subjects
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Listing 16.2.7.1	All Adverse Events	All Randomized Subjects
Listing 16.2.7.2	Serious Adverse Events	All Randomized Subjects
Listing 16.2.7.3	Adverse Events Leading to Study Drug Discontinuation	All Randomized Subjects
Listing 16.2.8.1	Best Corrected Visual Acuity	All Randomized Subjects
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Listing 16.2.8.3	Intraocular Pressure (mmHg)	All Randomized Subjects
Listing 16.2.8.4	Dilated Ophthalmoscopy	All Randomized Subjects
Listing 16.2.8.5	Physical Examination	All Randomized Subjects
Listing 16.2.8.6	Vital Signs	All Randomized Subjects
Listing 16.2.8.7	Urine Pregnancy Test Results - Female Subjects Only	All Randomized Subjects

Listing 16.2.9	In-Office Study Drug Instillation Comfort Score and Questionnaire	All Randomized Subjects