Systane® Ultra Preservative Free Lubricant Eye Drops

STUDY ID

DEU894-I001

STATISTICAL ANALYSIS PLAN

NCT05902364

Statistical Analysis Plan

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STUDY TITLE:

SYSTANE® ULTRA PRESERVATIVE FREE LUBRICANT EYE DROPS

SPONSOR:

Alcon Research LLC

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Fort Worth, Texas 76134-2099, USA

Researchers are conducting this study in compliance with good clinical practice, including archiving of essential documentation.

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List of Abbreviations

Abbreviation	Description
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CL	Contact Lens
CLDEQ-8	Contact Lens Dry Eye Questionnaire
CSR	Clinical Study Report
DE	Dry Eye
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
IC	Informed Consent
IDEEL-SB	Impact of Dry Eye on Everyday Life - Symptom Bother
FAS	Full Analysis Set Population
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
OD	Oculus Dexter/Right Eye
OS	Oculus Sinister/Left Eye
PMCF	Post-Market Clinical Follow-Up
PF	Preservative Free
PP	Per-Protocol Population
PT	Preferred Term
Q1	First Quartile, 25th Percentile
Q3	Third Quartile, 75th Percentile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TFOS	Tear Film and Ocular Surface Society
VA	Visual Acuity
US	United States

1. Study Objectives and Design

1.1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses ICON plc will conduct as a part of Alcon's Protocol DEU894-I001 for inclusion in the Clinical Study Report (CSR). The content of this SAP is based on Protocol V2.0 dated 26 October 2023. ICON plc will document any small deviations from the analyses outlined in this plan with rationale in the final CSR. Any major changes to the conduct of the study will be recorded in a protocol amendment and SAP change log.

ICON PLC will perform the statistical analyses and is responsible for the production and quality control of all tables, listings and figures.

This post-market clinical follow-up (PMCF) study aims to assess the performance and safety of Systane Ultra Preservative Free (PF) in adult subjects (≥ 18 years) experiencing mild to moderate dry eye disease (DED) and contact lens (CL) wearers who experience discomfort due to CL-related dryness outside the United Sates (US), where the product is commercially available.

1.2. Study Objectives

PRIMARY OBJECTIVES:

The primary objectives of this PMCF study is to assess the performance and safety of Systane Ultra PF in subjects experiencing dry eye symptoms (DE) [Group 1] and CL wearers experiencing discomfort due to CL-related dryness (Group 2).

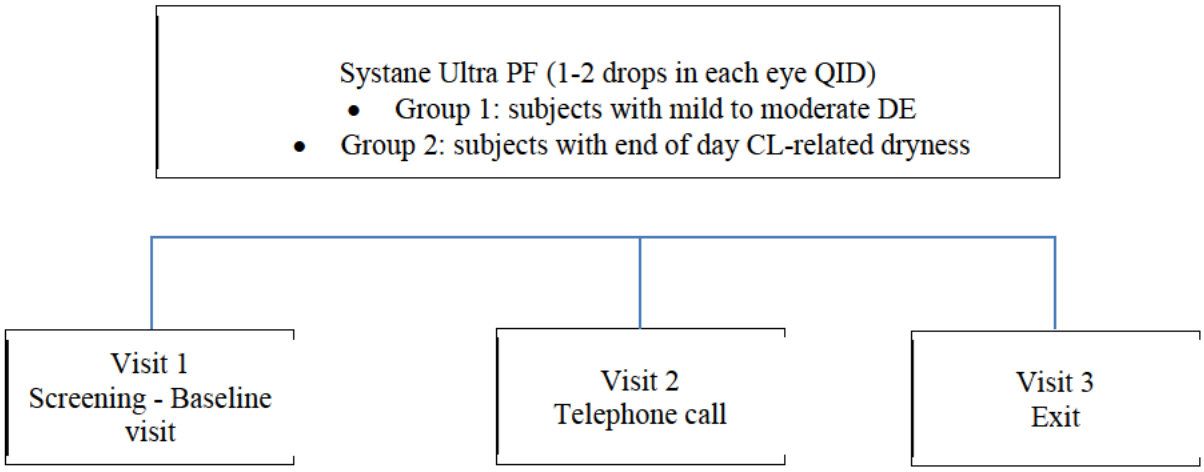
1.3. Study Descriptions

1.3.1. Overview of Study Design

This is a post-market, multicenter, non-comparative, single arm, open-label, prospective clinical study to assess the performance and safety of Systane Ultra PF in adult subjects experiencing DE symptoms and CL wearers experiencing discomfort due to CL-related dryness.

The study will be conducted outside the US, where the product is commercially available, in clinical sites known to routinely manage subjects with dry eye disease (DED) and CL wearers.

Figure 1: Overall Study Design.



CL: Contact lens; QID: Four times a day.

Systane Ultra PF will be dispensed at Screening/Baseline visit. Subjects will be expected to attend one additional visit at Day 30 (±2days) after screening and a telephone call visit at Day 15 (±2days).

Eligible subjects will initiate treatment with Systane Ultra PF at the Screening/Baseline visit and will be required to self-administer Systane Ultra PF four times daily up to Visit 3. The dose selected in this study is the dose approved for Systane Ultra PF for the management of DED.

As shown in Figure 1, subjects will participate in the study for approximately 30 days, with a phone call scheduled on Day 15 ± 2 (Visit 2) and a follow-up visit scheduled on Day 30 ± 2 (Visit 3). Subjects may have unscheduled visits if deemed necessary per the Investigator's judgment.

Subjects will be asked to complete subject questionnaires on Day 1 and at Visit 3 (Impact of Dry Eye on Everyday Life - Symptom Bother [IDEEL-SB] or Contact Lens Dry Eye Questionnaire [CLDEQ-8] [redacted] In addition, subjects will be instructed to document Systane Ultra PF dosing information on a daily basis using a subject diary.

The overall study duration (first subject screened to last subject's final study visit) is expected to be approximately 2 months.

The schedule of study assessments is presented in Table 1.

Table 1: Data Collection Schedule

Procedure/Assessment	Visit 1 Screening / Baseline (Day 1)	Visit 2 (phone) 15-day Follow-up (±2 days)	Visit 3 30-day / Exit (±2 days)	Unscheduled Visit / Early Exit
Informed consent (IC)	X			
Demographics	X			
Targeted medical history	X			
Targeted concomitant medications	X			
IDEEL-SB questionnaire[a]	X		X	(X)
CLDEQ-8 questionnaire[b]	X		X	(X)
[redacted]	[redacted]		[redacted]	[redacted]
Inclusion/Exclusion	X			
Changes in concomitant medications		X	X	X
Best Corrected Visual Acuity (BCVA)	X		X	(X)
[redacted]	[redacted]		[redacted]	[redacted]
Biomicroscopy (include corneal staining)	X		X	(X)
Adverse events (AEs)	X	X	X	X
Device deficiencies	X	X	X	X
Exit form	(X)		X	X
Telephone follow-up for compliance check		X		

(X) assessment performed as necessary

[a] Assessed in Group 1 only (subjects with mild to moderate DE)

[b] Assessed in Group 2 (subjects with end of day CL-related dryness)

1.3.2. Study Population

The study population consists of adult male and female subjects (≥18 years) with mild to moderate DED and CL wearers who experience discomfort due to CL related dryness. Subjects will be selected based on the inclusion criteria and exclusion criteria listed in Sections 6.4.4 and 6.4.5 of the protocol.

1.4. Randomization

Randomization is not applicable for this study.

1.5. Masking

This study is open-label.

1.6. Interim Analysis

No interim analyses are planned.

2. Analysis Sets

Two analysis sets will be defined for this study as outlined below.

2.1. Full Analysis Set (FAS)

The FAS will include all subjects/eyes exposed to at least one dose of Systane Ultra PF. The FAS will serve as the primary analysis set for all effectiveness and safety analyses.

2.2. Per-Protocol (PP)

The PP is a subset of the FAS and will exclude subjects with major protocol deviations. The PP population will be used as a supportive set for primary [redacted] analyses if the protocol deviation subjects exceed 5%. Major protocol deviations leading to the exclusion from PP population will be identified in the "Protocol Deviation Criteria Form".

3. General Aspects for Statistical Analysis

3.1. General Methods

In general, summaries will present data overall and by the following groups:

- Group 1: subjects with mild to moderate DE receiving Systane Ultra PF.
- Group 2: subjects with end of day CL-related dryness receiving Systane Ultra PF.

No hypothesis testing will be performed. Whenever applicable, 95% confidence intervals (CIs) will be provided. For proportions, 95% CIs will be calculated using the exact Binomial (Clopper-Pearson) method [1]. 95% CIs of a normal distribution for means will be provided, as needed.

All relevant subject data will be included in listings. The listings will be sorted by subject ID, and other characteristics (age, sex, eye(s), etc.), if necessary.

Data collected for IDEEL-SB, CLDEQ-8, [redacted], BCVA, [redacted] and Biomicroscopy findings at unscheduled visits may be included in by-visit summaries and analyzed in the same fashion as the data collected at scheduled visits except where otherwise noted.

SAS® version 9.4 or higher will be used for all statistical analyses and tabulations.

3.2. Rules for Reporting Statistics

Continuous variables will be summarized using descriptive statistics, i.e., by the number of non-missing observations (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum. Where specified in the table shells, the number of missing observations and 95% CI for the mean will also be provided.

For reporting conventions:

- The number of non-missing and missing observations will be presented as whole numbers.
- The minimum and maximum will be presented with the same number of decimal places as presented in the data.
- The mean (and correspondent 95% CI), median, Q1 and Q3 will generally be displayed with one more decimal place than presented in the data.
- The SD will generally be displayed with 2 more decimal places than the raw data. If there is only one observation (n=1), the SD will be displayed as a hyphen ("-").
- If there is no observation, summary statistics will be displayed with a hyphen ("-").

Qualitative variables will be summarized by frequency counts (n) and percentages (%). Unless otherwise stated, the calculation of proportions/percentages for a given qualitative variable will exclude subjects/eyes with missing values from the denominator.

For reporting conventions, percentages will be reported to one decimal place unless greater precision is deemed appropriate, except for cases when 100% is presented. In cases of a count of 0, the percentage will not be presented.

In case the analysis refers only to certain visits/timepoints, summary statistics and percentages will be based on the number of subjects/eyes having available result at each visit/timepoint.

Summaries on change from Baseline by visit/timepoint will be based on subjects/eyes who have both baseline and post-baseline values at the visit/timepoint being summarized.

3.3. Key Definitions

Enrolled subjects are defined as all subjects who provided signed IC.

Eligible subjects are defined as all subjects who provided signed IC and met all the eligibility criteria for this study.

Baseline is defined as the last non-missing value prior to the start date of the study treatment. For non-treated subjects, baseline is defined as the value from the Visit 1 (Screening).

Study Day 1 is defined as the first day of study treatment administration. Study day will be calculated as date of event/collection – first dose date of the study treatment + 1 for all assessments after start of study treatment and as date of event/collection – first dose date of the study treatment for all assessments prior to start of device use.

End of study date is defined as the date of the latest of the following events:

- Date of early termination collected from the "Subject Disposition" eCRF form (not use if reason for discontinuation is lost to follow-up).
- Last contact date among the following dates (only completed dates) collected on the eCRF:
    - Subject assessment dates (e.g., questionnaires, slit lamp biomicroscopy, [redacted] BCVA).
    - AE start and end dates.
    - Device deficiency dates.
    - Visit dates (only performed visits).
    - Study treatment start and end dates.

3.4. Missing Data

Unless otherwise specified in this SAP, all data will be evaluated as reported in the database and no imputation for missing values will be done, except for AEs dates. Handling of partial dates is described in Appendix 13.1.

3.5. Analysis Visit Windows

As per the protocol, data will be collected for the assessments at the Screening/Baseline (Visit 1), 15-day Follow-up (Visit 2), and 30-day/Exit (Visit 3). The data will be collected within ±2 days window for the Visit 2 and Visit 3. By-visit summaries will use the analysis visit. Scheduled, unscheduled and early termination visits will be windowed based on the following analysis visit window (Table 2).

1) If the scheduled records do not fall within a visit window, then the records will be flagged as out of the allowed window and the original visit from the eCRF will be assigned for the analysis visit. In case of unscheduled records not falling within a visit window, the original visit from the eCRF will be assigned.
2) For post-baseline visits, if there is more than 1 record available within the same visit window, the following rules will be applied:
    a. Select the record collected at the scheduled visit.
    b. If there are no records at the scheduled visit, then the record closest to the target day will be used.
    c. If there are multiple records with the same distance to the target day, the latest record will be used.
3) For Baseline visit, the last non-missing record among scheduled and unscheduled assessments will be selected.

Table 2: Analysis Visit Window

Analysis Visit	Target Study Day	Visit Window for IDEEL-SB, CLDEQ-8, [redacted] BCVA, [redacted] Biomicroscopy
Baseline	1	<=1
Visit 2	15	13 to 17
Visit 3	30	28 to 32

In general, only observations assigned to an analysis visit window will be included in the analysis. Data collected at unscheduled visits will be included in the data listings. In addition, any data collected out of the allowed window will be flagged in the listings.

3.6. Pooling of Centers

Summaries will be provided pooled for all sites overall and by group if not indicated otherwise.

4. Subject Characteristics

4.1. Subject Disposition

Summary table reflecting subject disposition will present:

- Number of enrolled subjects (only for overall).
- Number of non-eligible subjects (any eligibility criteria not met) [only for overall].
- Number of subjects by reason for ineligibility (only for overall): inclusion criteria not met; exclusion criteria met.
- Number (%) of eligible subjects.
- Number (%) of subjects who completed the study.
- Number (%) of subjects who discontinued the study with reasons for early study termination.
- Length of follow-up (days).
- Number (%) of subjects included in each analysis set (FAS and PP).

Supportive listings will be provided for subject disposition and study visits.

Derivations:

- Length of follow-up (days) = end of study date – date of first dose of study treatment + 1.

Note: For subjects who are still ongoing in the study at the time of the analysis, the end of study date will be imputed as the data cut-off date.

4.2. Protocol Deviations

Analysis Set: FAS

Protocol deviations will be identified periodically throughout the study based on the "Protocol Deviation Criteria Form". This form is transferred before each analysis indicating subject with protocol deviations as reason of exclusion from PP. Major protocol deviations that lead to the exclusion from PP will be summarized. All protocol deviations will be listed.

4.3. Demographics and Clinical Characteristics at Baseline

Analysis Set: FAS

Demographic and clinical characteristics at Baseline will be summarized using the information collected from the screening data. Demographic and clinical characteristics will include:

- Age (years).
- Age categories: >=18 years to <30 years, >=30 years to <50 years, >=50 years to <70 years and >=70 years.
- Sex: Male, Female, Unknown, Unconfirmed.
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Unknown, Unconfirmed.
  Note: An additional category "Mixed" will be created for subjects with more than one race reported.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Unconfirmed.
- IDEEL-SB symptoms score (only Group 1).
- CLDEQ-8 score (only Group 2).
- [redacted]
- BCVA score (logMAR) [eye-level summary].

A supportive listing for demographic and clinical characteristics will be provided.

4.4. Targeted Medical History

Medical conditions within 1 year prior to the Screening (Visit 1) will be collected from "Targeted Medical History and Concomitant Medication" eCRF form.

Any preexisting medical conditions or signs/symptoms present in a subject prior to the start of the study (i.e., before IC is signed) are not considered AEs in the study and should be recorded in the Medical History section of the eCRF.

A supportive listing for medical history will be provided.

4.5. Targeted Concomitant Medication

Concomitant medications taken within the past 30 days prior to the Screening/Baseline (Visit 1) will be listed.

4.6. Treatment Duration and Missed Doses

The frequency (number and percentage) of subjects with at least one missed dose during the study and the treatment duration (in days) will be summarized.

Derivations:

- Treatment duration (days) = date of last dose of study treatment – date of first dose of study treatment + 1.

Note: For treatment duration calculation, if the date of last dose of study treatment is unknown at the time of the analysis, it will be imputed as the end of study date (for subjects who complete or discontinue the study at the time of the analysis) or the data cut-off date (for subjects who are still ongoing in the study).

5. Efficacy Analysis Strategy

This study defines one primary effectiveness endpoint [redacted] The FAS will be used for all effectiveness analyses. The PP population will be the supportive analysis set for primary [redacted] analyses.

All endpoints will be summarized overall and by groups as defined in Section 3.1.

No imputation for missing values will be carried out for the primary and supportive effectiveness analyses.

[redacted].

5.1. Efficacy Endpoints

PRIMARY EFFECTIVENESS ENDPOINT:

The primary effectiveness endpoint is:

- Group 1: Dry eye (DE) questionnaire via IDEEL-SB at Baseline and at Visit 3
- Group 2: DE questionnaire via CLDEQ-8 at Baseline and at Visit 3

[redacted]

5.2. Efficacy Hypotheses

There are no statistical hypotheses in this study. [redacted]

5.3. Statistical Methods for Efficacy Analyses

5.3.1. Primary Effectiveness

Group 1:

DES will be assessed using the IDEEL-SB questionnaire (see Appendix 13.2) at the Screening/Baseline visit (Day 1) before Systane Ultra PF use, and at Visit 3 (and at unscheduled and at early exit visits, as necessary).

The primary effectiveness endpoint is the IDEEL-SB score. The IDEEL-SB score is calculated by the mean value of the non-missing item scores multiplied by 25, with a higher score indicating greater satisfaction and less treatment-related bother.

The primary effectiveness endpoint will be summarized as a continuous variable at each analysis visit (Baseline and Visit 3). The mean IDEEL-SB score will be presented together with the corresponding 95% CI. [redacted]

Group 2:

CL symptoms will be assessed using the CLDEQ-8 questionnaire (see Appendix 13.3) at the Screening/Baseline visit (Day 1) before Systane Ultra PF use, and at Visit 3 (and at unscheduled and at early exit visit, as necessary).

The primary effectiveness endpoint is the CLDEQ-8 score. The CLDEQ-8 score is calculated by the sum of the non-missing item questions.

The primary effectiveness endpoint will be summarized as a continuous variable at each analysis visit (Baseline and Visit 3). The mean CLDEQ-8 score will be presented together with the corresponding 95% CI. [redacted]

Derivations:

- IDEEL-SB score = (Sum of (Item 1,…, Item 20) / n) x 25, where n = number of items with non-missing answer.
- CLDEQ-8 score = Sum of (Question 1,…, Question 8).

[redacted]

5.4. Handling Missing Data

Missing data for primary [redacted] effectiveness endpoints will not be imputed. The IDEEL-SB score is calculated if at least 50% (10 items) of the 20 items within the dimension are completed (non-missing), otherwise the score is set to missing.

5.5. Multiplicity Strategy

No multiplicity adjustment needs to be considered for the effectiveness endpoints since no formal hypothesis testing will be conducted.

5.6. Subgroup Analysis and Effect of Baseline Factors

No subgroup analyses are currently planned.

5.7. Interim Analysis for Efficacy

No interim analyses for effectiveness endpoints are currently planned.

6. Safety Analysis Strategy

The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of AE as well as the other listed parameters. Therefore, no inferential testing will be done for the safety analysis.

6.1. Safety Endpoints

The safety endpoints for this study are:

- Biomicroscopy findings (including corneal staining)
- BCVA
- AEs
- Device deficiencies

6.2. Safety Hypotheses

No inferences are to be made on the safety endpoints; therefore, no hypotheses are formulated.

6.3. Statistical Methods for Safety Analyses

The FAS will be used for all safety analyses. All safety endpoints will be summarized descriptively overall and by group.

6.3.1. Adverse Events

The applicable definition of an AE is in the study protocol. All AEs will be collected from the time of signed IC until study participation is complete. AEs will be coded using the most current available version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of the data-cut.

All analyses described will be based on treatment-emergent adverse events (TEAEs), if not otherwise specified. TEAEs are those events with onset dates occurring on or after the first dose of study treatment until the end of the study. AEs with an onset date missing will be considered as TEAE.

- **AEs related with study device**: AEs recorded on the AE eCRF page, Relationship to Study Device = Related) and those of unknown relationship (i.e., no answer to the question “Relationship to Study Device”).
- **AEs related with test procedure**: AEs recorded on the AE eCRF page, Relationship to Test Procedure = Related) and those of unknown relationship (i.e., no answer to the question “Relationship to Test Procedure”).
- **Serious adverse events (SAEs)**: AEs recorded on the AE eCRF page, Was this a Serious Adverse Event? = Yes.

- **AEs resulting in study device permanent discontinuation:** AEs recorded on the AE eCRF page, Action Taken Due To Adverse Event = Study Device Permanently Discontinued.
- **AEs resulting in death**: AEs recorded on the AE eCRF page, Death = Yes or Outcome = Fatal.
- **Ocular AEs**: AEs recorded on the AE eCRF page, Eye = OD or OS.

TEAEs will be summarized as the number and percentage of subjects/eyes by MedDRA Preferred Terms (PT) as an event category. Each subject/eye will be counted only once within a given PT. TEAEs will be displayed in terms of frequency tables sorted on decreasing frequency of PT. In case of equal frequency regarding PT, alphabetical order will be used. In case any specific TEAE does not have MedDRA PT coded terms, it will be summarized under the "Uncoded" category.

The following tables will be created for non-ocular TEAEs (subject-level summary):

- The overall summary table of non-ocular TEAEs will include the number of non-ocular TEAEs and the frequency (number and percentage), and the corresponding 95% CI of subjects with:
    - Any non-ocular TEAE
    - Any moderate non-ocular TEAE
    - Any severe non-ocular TEAE
    - Any non-ocular TEAE related with study device
    - Any non-ocular TEAE related with test procedure
    - Any serious non-ocular TEAE
    - Any serious non-ocular TEAE related with study device
    - Any serious non-ocular TEAE related with test procedure
    - Any non-ocular TEAE resulting in study device permanent discontinuation
    - Any non-ocular TEAE resulting in death
- Non-ocular TEAEs by PT
- Serious non-ocular TEAEs by PT
- Non-ocular TEAEs related with study device by PT

For ocular TEAEs, the following data will be summarized (eye-level summary):

- The overall summary table of ocular TEAEs will include the number of ocular TEAEs and the frequency (number and percentage), and the corresponding 95% CI of eyes with:
    - Any ocular TEAE
    - Any moderate ocular TEAE
    - Any severe ocular TEAE
    - Any ocular TEAE related with study device
    - Any ocular TEAE related with test procedure
    - Any serious ocular TEAE
    - Any serious ocular TEAE related with study device
    - Any serious ocular TEAE related with test procedure
    - Any ocular TEAE resulting in study device permanent discontinuation
    - Any ocular TEAE resulting in death
- Ocular TEAEs by PT
- Serious ocular TEAEs by PT
- Ocular TEAEs related with study device by PT

Supportive listings will be provided for all TEAEs. Ocular TEAEs will be flagged.

6.3.2. BCVA

BCVA will be assessed per standard practice at the Screening/Baseline visit (Day 1) and at Visit 3 (and at unscheduled and early exit visits, as necessary).

For each eye, the distance visual acuity (VA) will be collected as per the site's standard of care practice using charts validated for the specific testing distance, which may include for example, 6 m for Snellen chart, 20 ft for Snellen chart, decimal chart and logMAR score. The values for BCVA will be presented in logMAR. BCVA will be summarized as a continuous variable at each analysis visit (Baseline and Visit 3) [eye-level summary]. The mean BCVA score will be presented together with the corresponding 95% CI. In addition, the change from Baseline will be summarized at Visit 3.

A supportive listing for BCVA assessments will be provided.

Derivations:

- BCVA (logMAR) = $-\log_{10}$ (20 / Snellen VA 20 ft fractions) if measured in 20 ft for Snellen chart.
- BCVA (logMAR) = $-\log_{10}$ (6 / Snellen VA 6 m fractions) if measured in 6 m for Snellen chart.
- BCVA (logMAR) = $-\log_{10}$ (decimal acuity) if measured in decimal chart.

6.3.3. Biomicroscopy Findings

Slit lamp biomicroscopy assessments will be performed using the ISO11980 grading at the Screening/Baseline visit (Day 1) and at Visit 3 (and at unscheduled and early exit visits, as necessary).

Biomicroscopy parameters will be summarized [eye-level summary] using descriptive statistics by analysis visit:

- Limbal Hyperemia: None, Trace, Mild, Moderate and Severe.
- Bulbar Hyperemia: None, Trace, Mild, Moderate and Severe.
- Corneal Epithelial Edema: None, Trace, Mild, Moderate and Severe.
- Corneal Stromal Edema (only Group 2): None, Trace, Mild, Moderate and Severe.
- Corneal Vascularization: None, Trace, Mild, Moderate and Severe.
- Conjunctival Compression/Indentation (only Group 2): Absent, Present.
- Chemosis: Absent, Present.
- Corneal Infiltrates (only Group 2): None, Trace, Mild, Moderate and Severe.
    - Central: Yes, No.
    - Peripheral Superior: Yes, No.
    - Peripheral Inferior: Yes, No.
    - Peripheral Nasal: Yes, No.
    - Peripheral Temporal: Yes, No.
    - Type: Focal, Diffuse.
    - Depth of Largest Infiltrate: Epithelial, Anterior stromal, Mid/posterior stromal.
    - Number of Infiltrates: 1, 2, 3, 4, 5, 6, 7, >=8.
    - Size of the Largest Infiltrate (mm).
- Corneal Staining: Absent, Present.
    - Central: None, Trace, Mild, Moderate and Severe.

  - Superior: None, Trace, Mild, Moderate and Severe.
  - Nasal: None, Trace, Mild, Moderate and Severe.
  - Inferior: None, Trace, Mild, Moderate and Severe.
  - Temporal: None, Trace, Mild, Moderate and Severe.
- Conjunctival Staining: None, Trace, Mild, Moderate and Severe.
- Palpebral Conjunctival Observations: None, Trace, Mild, Moderate and Severe.
- Other Findings: None, Trace, Mild, Moderate and Severe.

Shift tables will be generated using the ISO11980 grading categories. The number and percentage of eyes shifting from categories between Baseline and Visit 3 will be summarized.

A supportive listing for biomicroscopy assessments will be provided.

6.3.4. Device Deficiencies

Device deficiencies will be collected at the time points specified in Table 1. The number of device deficiencies reported during the study will be tabulated.

A supportive listing will be provided.

6.4. Other Safety Endpoints

Not Applicable.

7. Analysis Strategy for Other Endpoints

7.1.1. Pregnancy

Information on pregnancy during the study will be listed for female subjects with childbearing potential or female subjects who become pregnant during the course of the study. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

7.1.2. Contact Lenses

For Group 2, information on type of contact lenses used will be listed.

8. Sample Size and Power Calculations

The study will recruit 68 subjects with a target to complete 54 evaluable subjects (27 in Group 1 and 27 in Group 2).

With a sample size of 54, a two-sided 95% CI for a single proportion will extend 0.060 from the observed proportion when the expected proportion is 0.0543 (AEs). Table 3 presents the precision for various rates of categorical outcomes.

Table 3: Precision for Various Percentages

Sample Size	Precision (%) for Various Rates of Outcomes			
	5%	10%	25%	50%
27	8.22%	11.32%	16.33%	18.86%
54	5.81%	8.00%	11.55%	13.34%

Precision calculated according to a simple asymptotic formula for a 2-sided 95% CI for a proportion based on the normal approximation of the binomial distribution.

9. Quality Control and Version Control

The Statistical Analyst will direct the project team to apply quality control and data validation programming to ensure consistency and accuracy of the statistical analysis datasets, statistical analyses, and associated output, according to ICON standard operating procedures [redacted] review involves, but is not limited to the following: generation of QC statistics, checking calculations of derived variables, confirmation of analytic cohort, examination of the SAS® LOG or equivalent, confirmation of statistical validity, and consistency of output across tables, listings, and figures.

ICON plc will designate the initial version of the SAP approved by the Sponsor and ICON plc as Version 1.0. ICON plc will document any changes made to the SAP in a new version and the version number updated. ICON plc may complete revisions to SAP attachments without requiring additional revisions and approval to the SAP.

10. References

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12. Appendix

12.1. Handling of Partial Dates

Incomplete AE onset date will be imputed as follows:

- If the AE onset date is completely missing, then no imputation will be performed, and the AE will be considered as TEAE.
- If the day of the AE onset date is missing, but the month and year are equal to the start date of study treatment, then the AE onset day will be replaced by the day of the start date of study treatment.
- If both the day and month of the AE onset date are missing but the onset year is equal to the year of study treatment start date, then the AE onset month and day will be replaced by the month and day of study treatment start date.
- In all other cases, the missing AE onset day or missing AE onset month will be replaced by 1.

Incomplete AE end date will be imputed as follows:

- If the AE end date is completely missing and the AE is not ongoing, then the AE end date will be replaced by the end of study date. If the end of study date is missing, then AE end date will not be imputed.
- If only the day of the AE end date is missing, then AE end day will be replaced by the last day of the month, if not resulting in a date later than the end of study date.
- If both the day and month of the AE end date are missing, then no imputation will be performed.

12.2. IDEEL-SB Questionnaire

Symptom Bother

These questions ask about the symptoms you may experience due to dry eyes.

1. **OVER THE LAST TWO WEEKS**, how often did you experience dry eye symptoms?

None of the time	A little of the time	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

The following questions ask about how bothersome dry eye symptoms were to you **OVER THE LAST TWO WEEKS**. If you had the symptom, please choose **how much the symptom bothered you** (not at all, slightly, moderately, or very much). If you did not have the symptom over the last week, choose the "I did not have this symptom / Not applicable" box. Please choose only one box per question.

OVER THE LAST TWO WEEKS, how much did each of the following symptoms bother you?	I did not have this symptom / Not applicable	**OVER THE LAST TWO WEEKS, I had this symptom and it bothered me:**			
		Not at all	Slightly	Moderately	Very much
2. Eyes that felt gritty or sandy	☐	☐	☐	☐	☐
3. Felt like I needed to close my eyes even though I was not tired	☐	☐	☐	☐	☐
4. Burning or stinging eyes	☐	☐	☐	☐	☐
5. Tired eyes	☐	☐	☐	☐	☐
6. Blurry vision	☐	☐	☐	☐	☐
7. Itchy eyes	☐	☐	☐	☐	☐
8. Irritated eyes	☐	☐	☐	☐	☐
9. Eyes that felt like they had been scratched by something	☐	☐	☐	☐	☐
10. Eye dryness	☐	☐	☐	☐	☐

 1

OVER THE LAST TWO WEEKS, how much did each of the following symptoms bother you?	I did not have this symptom / Not applicable	**OVER THE LAST TWO WEEKS, I had this symptom and it bothered me:**			
		Not at all	Slightly	Moderately	Very much
11. Mucus in, around, or coming out of my eyes	☐	☐	☐	☐	☐
12. Puffy or swollen eyes	☐	☐	☐	☐	☐
13. Eye redness	☐	☐	☐	☐	☐
14. Aching or sore eyes	☐	☐	☐	☐	☐
15. Felt like something was in my eye	☐	☐	☐	☐	☐
16. Frequent and/or rapid blinking	☐	☐	☐	☐	☐
17. Difficulty blinking because of little or no moisture in my eyes	☐	☐	☐	☐	☐
18. Sensitivity to light, glare, and/or wind	☐	☐	☐	☐	☐
19. Sensitivity to re-circulated air (such as air conditioning and heat)	☐	☐	☐	☐	☐
20. Headaches associated with dry eye symptoms	☐	☐	☐	☐	☐

Thank you for finishing this questionnaire.
Please make sure that you answered every question.

 2

Administration and Scoring

A paper copy of the IDEEL-SB module will be given to each subject for completion without assistance.

Question 1 is scored on a 5-point Likert-type scale where 0 = None of the time, 1 = A little of the time, 2 = some of the time, 3 = Most of the time, and 4 = All of the time. Questions 2-20 are scored on a 4-point Likert-type scale where 0 = I did not have this symptom / Not Applicable, 1 = Not at all, 2 = Slightly, 3 = Moderately, 4 = Very much.

The subject will be instructed to select a single response that best represents their answer. The score is calculated if at least 50% (10 items) of the 20 items within the dimension are completed; non-missing; otherwise the score is set to missing. The Symptom Bother score is calculated as the mean value of the non-missing item scores 1-20 multiplied by 25.

$$\frac{\text{Sum of responses from questions 1- 20}}{\text{Number of questions (1-20) answered}} \times 25 = \text{IDEEL SB score}$$

The final calculated IDEEL-SB score for each subject will be entered into the study source documents to determine eligibility at the Screening Visit.

12.3. CLDEQ-8 Questionnaire

Patient/Subject #:_____
Date:__/__/____Time:_____

CONTACT LENS QUESTIONNAIRE-8 (CLDEQ-8)

1. Questions about **EYE DISCOMFORT**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel discomfort while wearing your contact lenses?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your eyes felt discomfort with your contact lenses, **how intense was this feeling of discomfort…**

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel dry?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your eyes felt dry, **how intense was this feeling of dryness**…

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

3. Questions about **CHANGEABLE, BLURRY VISION:**

   a. During a typical day in the past 2 weeks, **how often** did your vision change between clear and blurry or foggy while wearing your contact lenses?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your vision was blurry, **how noticeable was the changeable, blurry, or foggy vision** …

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

4. Question about **CLOSING YOUR EYES:**
   During a typical day in the past 2 weeks, **how often** did your **eyes bother you so much that you wanted to close them**?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

5. Question about **REMOVING YOUR LENSES:**
   How often during the past 2 weeks, did your eyes *bother you so much* while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and **take out your contact lenses**?

   1 Never
   2 Less than once a week
   3 Weekly
   4 Several times a week
   5 Daily
   6 Several times a day

13. Tables, Listings, and Figures

A separate document contains the shells to be employed in this study.

Table 14.1.1.1.1: Subject Disposition

Table 14.1.1.1.2: Subject Disposition by Site

Table 14.1.2.1.1: Major Protocol Deviations – FAS

Table 14.1.3.1.1: Summary of Demographics and Baseline Clinical Characteristics – FAS

Table 14.1.3.1.2: Summary of Demographics and Baseline Clinical Characteristics by Site – FAS

Table 14.1.4.1: Summary of Treatment Duration and Missed Doses – FAS

Table 14.2.1.1.1.1: Summary of IDEEL-SB Score by Analysis Visit (Group 1) – FAS

Table 14.2.1.1.1.2: Summary of IDEEL-SB Score by Analysis Visit (Group 1) – PP

Table 14.2.1.2.1.1: Summary of CLDEQ-8 Score by Analysis Visit (Group 2) – FAS

Table 14.2.1.2.1.2: Summary of CLDEQ-8 Score by Analysis Visit (Group 2) – PP

Table 14.3.1.1: Overall Summary of Non-Ocular Treatment-Emergent Adverse Events (TEAEs) - FAS

Table 14.3.1.2.1: Summary of Non-Ocular Treatment-Emergent Adverse Events (TEAEs) by MedDRA PT – FAS

Table 14.3.1.2.2: Summary of Serious Non-Ocular Treatment-Emergent Adverse Events (TEAEs) by MedDRA PT – FAS

Table 14.3.1.2.3: Summary of Non-Ocular Treatment-Emergent Adverse Events (TEAEs) Related with Study Device by MedDRA PT – FAS

Table 14.3.1.3: Overall Summary of Ocular Treatment-Emergent Adverse Events (TEAEs) - FAS

Table 14.3.1.4.1: Summary of Ocular Treatment-Emergent Adverse Events (TEAEs) by MedDRA PT – FAS

Table 14.3.1.4.2: Summary of Serious Ocular Treatment-Emergent Adverse Events (TEAEs) by MedDRA PT – FAS

Table 14.3.1.4.3: Summary of Ocular Treatment-Emergent Adverse Events (TEAEs) Related with Study Device by MedDRA PT – FAS

Table 14.3.2.1: Summary of BCVA Score (logMAR) by Analysis Visit – FAS

Table 14.3.3.1: Summary of Biomicroscopy Findings by Analysis Visit – FAS

Table 14.3.3.2: Shift from Baseline to Visit 3 Biomicroscopy Findings – FAS

Table 14.3.3.3: Summary of Corneal Staining by Analysis Visit – FAS

Table 14.3.3.4: Shift from Baseline to Visit 3 Corneal Staining – FAS

Table 14.3.3.5: Summary of Corneal Infiltrates by Analysis Visit (Group 2) – FAS

Table 14.3.4.1: Summary of Device Deficiencies - FAS

Listing 16.2.1.1: Listing of Subject Disposition

Listing 16.2.1.2: Listing of Missed Visits – FAS

Listing 16.2.2.1: Listing of Protocol Deviations – FAS

Listing 16.2.3.1: Listing of Demographics and Baseline Clinical Characteristics – FAS

Listing 16.2.3.2: Listing of Medical History and Concomitant Medication – FAS

Listing 16.2.3.3: Listing of Missed Doses - FAS

Listing 16.2.4.1: Listing of IDEEL-SB Questionnaire (Group 1) – FAS

[redacted]

Listing 16.2.4.3: Listing of CLDEQ-8 Questionnaire (Group 2) – FAS

[redacted]

Listing 16.2.5.1: Listing of Treatment-Emergent Adverse Events (TEAEs) – FAS

Listing 16.2.6.1.1: Listing of BCVA Assessments – FAS

Listing 16.2.6.2.1: Listing of Biomicroscopy Findings – FAS

Listing 16.2.6.2.2: Listing of Corneal Staining Findings – FAS

Listing 16.2.6.2.3: Listing of Corneal Infiltrates Findings (Group 2) – FAS

Listing 16.2.6.3.1: Listing of Device Deficiencies – FAS

Listing 16.2.6.4.1: Listing of Pregnancy – FAS

Listing 16.2.6.5.1: Listing of Contact Lenses (Group 2) – FAS