Systane® Complete Preservative Free Lubricant Eye Drops

STUDY ID

DEC262-I001

PROTOCOL

NCT05932225

Systane® Complete Preservative Free Lubricant Eye Drops
Version 1.0 / 24 April 2023

Sponsor:	Alcon Research LLC 6201 South Freeway Fort Worth, Texas 76134
Study Device:	Systane® Complete Preservative Free Lubricant Eye Drops
Protocol Identifiers:	DEC262-I001

Sponsor Approval:

[redacted]

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This document is a protocol for a human research study. This study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and according to International standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research prior to the enrollment of any subjects.

As Principal Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol, to provide documentation of my experience and qualifications to the Sponsor, to disclose any relevant financial interests or agreements related to the Sponsor or the investigation and to maintain study documentation for the period of time required.

I agree to personally conduct or supervise the described investigation. I agree to maintain adequate and accurate records and to make those records available for inspection by the Sponsor, its representatives, applicable regulatory authorities, and the IRB/IEC. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I certify that I have not been terminated from an investigation due to compliance failure (debarment).

_____ _____

Signature Date (DD MMM YYYY)

_____

Print Name/Title of Principal Investigator

VERSION HISTORY

Version	Approval Date	Significant Changes from Previous Version
1.0	24 April 2023	Original Protocol Version

CONFIDENTIALITY STATEMENT

The information contained in this document, especially unpublished data, is the property of Sponsor and therefore is confidential and may not be disclosed unless such disclosure is required by law or regulation. That Sponsor confidential information may be disclosed to the Investigator(s), potential Investigator(s) and necessary Investigator assistant(s) or study personnel. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them without written authorization from Sponsor. These restrictions on disclosure will apply equally to all future information supplied to the Investigator(s), potential Investigator(s) and necessary Investigator assistant(s) or study personnel, which is indicated as privileged or confidential.

Clinical Study Protocol

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STUDY SYNOPSIS

Title	**Systane Complete Preservative Free Lubricant Eye Drops**
Protocol Numbers	DEC262-I001
Study Sponsor	Alcon Research LLC 6201 South Freeway Fort Worth, Texas 76134
Study Design	Post-Market, multicenter, non-comparative, single arm, open-label, prospective clinical study
Study Duration	The overall study duration (first subject screened to last subject's final study visit) is expected to be approximately 2 months.
Study Centers	5 sites in the US and/or outside US, where the product is commercially available
Objectives	The objective of this post-market clinical follow-up (PMCF) study is to assess the performance and safety of Systane Complete Preservative Free (PF) Lubricant Eye Drops in subjects experiencing dry eye symptoms.
Number of Subjects	54 evaluable subjects Investigators will be asked to enroll approximately 22% of subjects with aqueous deficient dry eye (i.e., 12 subjects), 45% of subjects with evaporative dry eye (i.e., 24 subjects), and 33% of subjects with mixed dry eye (i.e., 18 subjects) as per the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II criteria for Dry Eye Disease (DED) stratification.
Main Inclusion / Exclusion Criteria	Subjects will be eligible to participate in the study if **all** of the following conditions exist: 1. Subject must be at least 18 years of age. 2. Subject must be able to understand and sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form. 3. Subject must be willing and able to attend all study visits as required per protocol. 4. Subject with mild to moderate dry eye (Impact of Dry Eye on Everyday Life - Symptom Bother [IDEEL SB] >16-64) 5. Subject must be willing to discontinue use of all habitual artificial tear supplements and use only the study device as directed for the entire study duration. 6. Subject using cyclosporine or other topical dry eye medications must be on a stable dosing regimen for ≥60 days prior to enrollment. Subjects will be excluded from participation in the study if any of the following conditions exist: 1. Has suffered any ocular injury to either eye in the past 3 months prior to screening 2. Has undergone any other ocular surgery (including intraocular surgery) within the past 6 months or has any ocular surgery planned during the study 3. Employee or family member of Investigators or Alcon 4. Currently enrolled in any clinical trial. 5. Use of any systemic medication known to cause dry eye (e.g., anti-histamine, anti-depressants, anti-psychotics, benzodiazepines, etc.) for less than 1 month before the Screening visit. If subject was on a stable regimen for at least a month prior to the Screening visit, the dosing regimen must not have changed for the duration of their participation in this study. In addition, subjects who did not currently use any of these medications could not start a regimen while participating in the study.

Study Device	Systane Complete PF Lubricant Eye Drops
Comparator	N/A
Endpoints	Primary effectiveness endpoints: • Dry eye questionnaire via IDEEL-SB at entry and at Visit 3 [redacted] Safety endpoints: • Biomicroscopy findings (include corneal staining) • Best corrected visual acuity (BCVA) • Adverse events (AEs) • Device deficiencies
Statistical Methods	Statistical analyses will be presented overall and by DED groups (aqueous deficient dry eye, evaporative dry eye, mixed dry eye). There is no statistical hypothesis for the endpoints in this study. Appropriate descriptive statistics will be computed and presented for all categorical and continuous endpoints. A full description of statistical methods will be presented in the Statistical Analysis Plan. • For categorical variables, the number and percentage of subjects/eyes within each category of interest will be presented. • For continuous variables, the number of subjects/eyes with non-missing data, mean, standard deviation, range, median, minimum, and maximum will be presented. • There will be no imputation for missing data. All visual acuity results will be presented in logarithm of the minimum angle of resolution (logMAR) scale after applying appropriate transformations/conversions.

ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ATP	Artificial tear products
BCVA	Best corrected visual acuity
CFR	Code of Federal Regulations
CRF	Case report form
DED	Dry eye disease
DES	Dry eye symptoms
DEWS	Dry eye workshop
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
FAS	Full analysis set population
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPCMS	Global Product Complaint Management System
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonization
IDEEL-SB	Impact of Dry Eye on Everyday Life - Symptom Bother
IEC	Independent Ethics Committee
IRB	Institutional Review Board
logMAR	Logarithm of the minimum angle of resolution
NaFl	Sodium fluorescein
[redacted]	[redacted]
PF	Preservative Free
PG-HPG	Propylene glycol-hydroxypropyl-guar
PHI	Protected Health Information
PI	Principal Investigator
PMCF	Post-market clinical follow-up
PP	Per-protocol population
SADE	Serious adverse device effect
SAE	Serious adverse event
SOP	Standard operating procedures
TFOS	Tear Film and Ocular Surface Society
US	United States

1 STUDY CONTACT INFORMATION

1.1 Sponsor Contact Information

[redacted]

1.2 Coordinating Principal Investigator Contact Information

The Coordinating Principal Investigator and coordinating institution will be listed in an attachment listing all participating sites.

1.3 Key Study Personnel

1.3.1 Clinical Study Monitor

The clinical study will be monitored by:

ICON Clinical Research
South County Business Park
Leopardstown
Dublin 18, Ireland

Clinical monitors will be assigned based on therapeutic area familiarity and availability.

1.3.2 Global Medical Safety Representatives

Medical safety oversight will be provided by Alcon Global Medical Safety Representatives.

1.3.3 Statistician

Biostatistical analysis will be provided by the ICON Clinical Research Biostatistics group.

2 INTRODUCTION / BACKGROUND AND RATIONALE

Dry eye disease (DED) is a common ocular disorder, which affects many individuals worldwide. The prevalence of DED with/without symptoms ranges from 5% to 50%; and based on signs alone, up to 75%.[1]

DED is characterized by a loss of homeostasis of the tear film resulting in ocular symptoms of discomfort, irritation, and visual disturbance, all of which significantly impact the patients' social and occupational quality of life.[2,3] Tear film insufficiency may be the result of inadequate aqueous tear production by the main and accessory lacrimal glands, excessive evaporation of the tears from the ocular surface, or a combination of both.[2]

Common factors associated with DED include elder age, female gender, and the presence of auto-immune disease. DED is also reported in younger and pediatric populations.[4,5] Other modifiable factors that can contribute to DED include the use of computers and digital devices, the use of heating, ventilation, and air conditioning systems, diet and lifestyle.[4]

While management of DED depends on the severity of symptoms and signs, use of artificial tear products (ATPs) that replace or supplement the deficient natural tear film is the mainstay treatment option.[6]

Systane Complete lubricant eye drops is a propylene glycol-hydroxypropyl-guar (PG-HPG) nanoemulsion, designed to replenish deficiencies in both the lipid and aqueous layers of the tear film.[7]

Systane Complete has been evaluated in several pre-clinical and clinical studies.[8] PG-HPG nanoemulsion lubricant eye drops have been shown to improve dry eye symptoms, enhance tear film stability, and lipid layer thickness; hence, they help to restore eye surface health and provide symptom relief in patients with DED, regardless of subtypes.

Systane Complete Preservative Free (PF) are eye drops formulated without preservatives.

This post-market clinical follow-up (PMCF) study aims to generate scientific evidence to address safety, performance, and clinical benefits of Systane Complete PF in subjects with DED.

3 STUDY DEVICE DESCRIPTION

Study device description is presented in Table 1.

Table 1. Study Device

Name	Systane Complete Preservative-Free
Formulation	Propylene glycol solution/drops
Unit dose strength	0.06 mg in 1 mL (0.6%)
Route of Administration	Ophthalmic
Supply Type **Packaging and Labeling**	Open label participant packs; bottles: 1 in 1 CARTON; 10 mL in 1 BOTTLE, DROPPER 2 in 1 CARTON; 10 mL in 1 BOTTLE, DROPPER Labeled as required per country requirement.
Storage Conditions	Store at room temperature

4 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The study device should be handled as per the instruction for use.

Subjects will be asked to return the study device at Visit 3. Sites will account for the return of the study device accordingly, and are expected to dispose/destroy the study device per the standard practice.

5 STUDY OBJECTIVES

The objective of this PMCF study is to assess the performance and safety of Systane Complete PF Lubricant Eye Drops in subjects experiencing dry eye symptoms.

6 STUDY DESIGN

6.1 Overview of Study Design

This is a post-market, multicenter, non-comparative, single arm, open-label, prospective clinical study.

The study will be conducted in the US and/or outside the US, where the product is commercially available, in clinical sites known to routinely manage patients with DED. The overall study duration (first subject screened to last subject's final study visit) is expected to be approximately 2 months.

Subjects will be enrolled into the study after signing the informed consent form (ICF).

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will initiate

treatment with Systane Complete PF. On Day 1, eligible study participants will be asked to instill one drop of Systane Complete PF in each eye on-site (during the Screening/Baseline visit) and the subsequent drop only after 8 hours (± 1 hour) at home. For the rest of the study duration (up to Visit 3), subjects will be asked to self-administer 1-2 drops in each eye; four times a day. The dose selected in this study is the dose approved for Systane Complete PF for the management of DED.

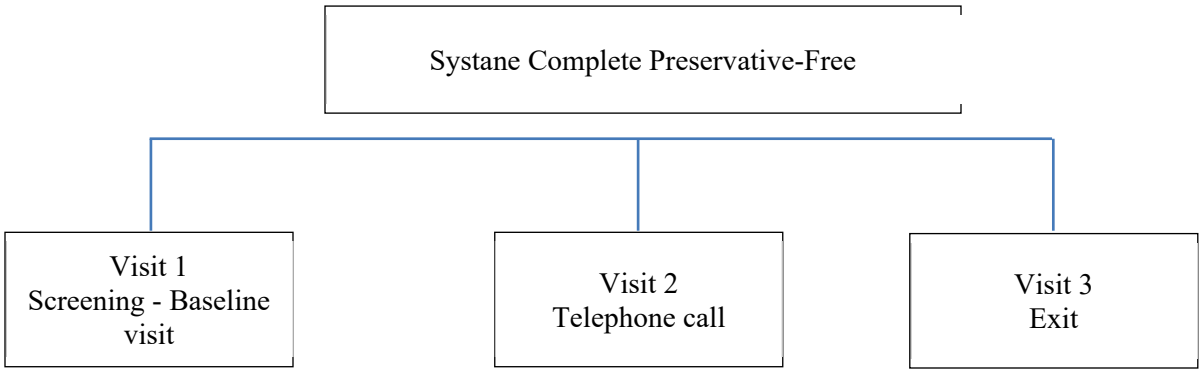
Subjects will participate in the study for approximately 30 days, with a phone call scheduled on Day 15 ± 2 (Visit 2) and a follow-up visit scheduled on Day 30 ± 2 (Visit 3). Subjects may have unscheduled visits if deemed necessary per the Investigator's judgment.

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

A summary of the study design is shown in Figure 1. Systane complete preservative-free dose regimen is shown in Figure 2. Study assessments are shown in the Schedule of Assessments (Table 4).

The study will enroll approximately 68 subjects with the objective of 54 subjects completing treatment with Systane Complete PF. Investigators will be asked to enroll approximately 22% of subjects with aqueous deficient dry eye (i.e., 15 subjects), 45% of subjects with evaporative dry eye (i.e., 31 subjects), and 33% of subjects with mixed dry eye (i.e., 22 subjects) as per the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II criteria for DED stratification.

Figure 1. Overall Study Design



Systane Complete Preservative-Free 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).

Figure 2. Systane Complete Preservative-Free Dose Regimen

Relative time	[Days]	Day 1		Day 2 → Day 30 (± 2 days)
	[Hours]	0 hours On site	8 hours (± 1) At home	-
	Dose	1 drop in each eye	1 drop in each eye	1-2 drops in each eye four times a day

6.2 Anticipated Duration of the Clinical Investigation

The anticipated duration of the clinical trial is approximately 2 months. The anticipated number of clinical sites is up to 5. This will result in an accrual rate of 6.8 subjects per site per month.

6.3 Effectiveness and Safety Endpoints

6.3.1 Primary Effectiveness Endpoint

- Dry eye questionnaire via IDEEL-SB at entry and at Visit 3

[redacted]

6.3.3 Safety Endpoints

- Biomicroscopy findings (include corneal staining)
- Best corrected visual acuity (BCVA)
- Adverse events (AEs)
- Device deficiencies

6.4 Study Population

The study population consists of adult male and female subjects (≥18 years old) with mild to moderate dry eye disease. Subjects will be recruited from clinical sites within and/or outside of the US, where Systane Complete Preservative-Free is commercially available.

6.4.1 Sample Size

The study will recruit 68 subjects with a target to complete 54 evaluable subjects.

With a sample size of 54, a two-sided 95% confidence interval for a single proportion will extend 0.060 from the observed proportion when the expected proportion is 0.0543 (AEs).

Table 2 presents the precision for various rates of categorical outcomes.

Table 2. Precision for Various Percentages

Sample Size	Precision (%) for Various Rates of Outcomes			
	5%	**10%**	**25%**	**50%**
54	5.81%	8.00%	11.55%	13.34%

Precision calculated according to a simple asymptotic formula for a 2-sided 95% confidence interval for a proportion based on the normal approximation of the binomial distribution.[9]

Investigators will be asked to enroll approximately 22% of subjects with aqueous deficient dry eye, 45% of subjects with evaporative dry eye, and 33% of subjects with mixed dry eye as per the TFOS DEWS II criteria.

6.4.2 Subject Recruitment

Subjects will be recruited from the clinical practices of the participating Investigators and surrounding metropolitan areas. Additional advertisement is not expected to be required.

6.4.3 Prior and Concomitant Therapy or Medications

Concomitant Medications

Targeted concomitant medications (see Section 7.3.2) must be recorded in source documents and on the appropriate electronic case report form (eCRF).

Prohibited Concomitant Medications

For subjects who meet all of the inclusion criteria and none of the exclusion criteria, the initiation of systemic medications known to cause dry eye (e.g., anti-histamine, anti-depressants, anti-psychotics, benzodiazepines, etc.) or known to treat dry eye (e.g., Restasis, Xiidra, Cequa) is not permitted during the study.

Rescue Medicine

Not applicable.

6.4.4 Inclusion Criteria

Subjects will be eligible to participate in the study if **all** of the following conditions exist:

1. Subject must be at least 18 years of age.
2. Subject must be able to understand and sign an IRB/IEC approved informed consent form.
3. Subject must be willing and able to attend all study visits as required per protocol.
4. Subject with mild to moderate dry eye (IDEEL SB >16-64).
5. Subject must be willing to discontinue use of all habitual artificial tear supplements and use only the study device as directed for the entire study duration.
6. Subject using cyclosporine or other topical dry eye medications must be on a stable dosing regimen for ≥60 days prior to enrollment.

6.4.5 Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

1. Has suffered any ocular injury to either eye in the past 3 months prior to screening
2. Has undergone any other ocular surgery (including intraocular surgery) within the past 6 months or has any ocular surgery planned during the study
3. Employee or family member of Investigators or Alcon
4. Currently enrolled in any clinical trial.
5. Use of any systemic medication known to cause dry eye (e.g., anti-histamine, anti-depressants, anti-psychotics, benzodiazepines, etc.) for less than 1 month before the Screening visit. If subject was on a stable regimen for at least a month prior to the Screening visit, the dosing regimen must not have changed for the duration of their participation in this study. In addition, subjects who did not currently use any of these medications could not start a regimen while participating in the study.

6.4.6 Exit / Discontinuation Criteria

Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- Screen failure
- AE/serious adverse event (SAE)
- Death
- Lack of efficacy
- Lost to follow-up
- Physician decision
- Protocol violation
- Study terminated by Sponsor or regulatory authority
- Technical problems with the study device
- Withdrawal by subject

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Exit Visit. The reason for subject withdrawal must be documented in the eCRF.

In the case of subject lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records. Withdrawn subjects will not be replaced.

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY PROCEDURES

7.1 Informed Consent

The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, International Conference on Harmonization (ICH) guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

A copy of the ICF must be provided to the subject.

7.2 Vulnerable Populations

Members of vulnerable populations will not be specifically targeted for recruitment. However, the intended subject population may include subjects who are considered to be vulnerable by definition. The procedures included in this protocol are sufficient to provide the necessary human subjects' welfare protections without the need for additional procedures.

7.3 Clinical Procedures and Assessments

After obtaining informed consent, assessments will be conducted for the enrolled subject as described in the sections below. The Investigator is responsible for ensuring that responsibilities for all assessments are delegated to appropriately qualified site personnel.

7.3.1 Demographics

Age, sex, race, and ethnicity will be collected at the Screening/Baseline visit (D1).

7.3.2 Medical History/Concomitant Medications

Fully document concomitant medications (taken within the past 30 days prior to the Screening/Baseline Visit) and Medical History (within 1 year prior to the Screening/Baseline

Visit) in the subject source documents (i.e., subject's chart). If the subject reports any condition in Table 3, the Investigator may ask for additional information at their discretion.

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

In the electronic data capture (EDC), only limited information regarding concomitant medications and medical history will be captured, as noted below.

- Medical History: Document all ocular history and targeted systemic history. In the EDC, there is a prepopulated dropdown field with items of interest that is consistent with Table 3.
- Concomitant medications: Document all ocular medications and targeted systemic medications used to treat conditions documented in Medical History and AEs.

Table 3. Targeted Medical History

Medical History	Definition
Active Respiratory Infections	• Principal respiratory viruses known to cause ocular disease in humans: o Adenovirus o Influenza virus o Respiratory syncytial virus o Coronavirus o Rhinovirus o Human metapneumovirus
Alcohol Abuse	• Heavy drinking: current or past consumption of ***4 or more*** servings of alcoholic beverages daily
Atopic Disease	• Atopy o Atopic dermatitis o Urticaria o Angioedema o Asthma o Allergic rhinitis
Cancer	• Cancers (potentially metastatic to eye or orbit), e.g., breast and lung cancer for women, gastrointestinal cancer for men, etc. • Cancers on active chemo- or radiotherapy
Diabetes Mellitus	• All Type I and II, some potential risk factors for retinopathy include: o Long duration o Insulin dependence o Increased Hemoglobin A1c levels o Elevated systolic blood pressure o Proteinuria o Decreased body mass index (BMI)
Headache	• Confirmed diagnosis (regardless of frequency of attacks) of: o Migraine with aura o Migraine without aura

Medical History	Definition
	○ Tension-type headache ○ Cluster headache • Headache with symptoms: ○ Systemic symptoms (e.g., fever, weight loss) ○ Neurologic symptoms/signs ○ Onset (sudden) ○ Older age (over 50 years) ○ Prior history (new headache) ○ Secondary illnesses (HIV or history of neoplasia)
Hypertension	• Chronic long-standing hypertension • Acute severe hypertension
HIV Infection	• Human immunodeficiency virus (HIV) disease with or without highly active antiretroviral therapy (HAART) • Low CD+ T-cell count (<100 cells /μL) is associated with severe ocular manifestations
Lupus	• Systemic Lupus Erythematosus (SLE) is a chronic, idiopathic, multisystem inflammatory disease characterized by hyperactivity of the immune system and prominent autoantibody production
Multiple Sclerosis	• Multiple sclerosis (MS) is a chronic relapsing and remitting, episodic demyelinating disease of the central nervous system
Rheumatoid Arthritis	• Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology that affects approximately 1% of the global population
Rosacea	• Rosacea with any subtype below: ○ Erythemato-telangiectatic ○ Papulopustular ○ Phymatous ○ Ocular rosacea
Sarcoidosis	• Sarcoidosis is a systemic inflammatory disease of unknown etiology characterized by the formation of noncaseating granulomas.
Scleroderma	• Systemic sclerosis sine scleroderma is a rare, chronic autoimmune disease with unknown etiology. Its prominent features are fibrosis, vasculopathy, and impaired immune response.
Seronegative spondyloarthropathies	• Ankylosing spondylitis • Reactive arthritis • Bechet's disease • Inflammatory bowel diseases • Psoriatic arthritis
Sjogren's Syndrome	• Primary Sjogren's syndrome • Secondary Sjogren's syndrome
Smoking	• Current smoker (regardless of number of pack-years) • Former smoker (cessation < 20 years before the study)
Systemic Herpes Zoster Infection	• A viral infection caused by varicella-zoster characterized by painful rash with blisters.
Thyroid Disorder	• Hyperthyroidism (e.g., Graves' disease) • Hypothyroidism (e.g., Hashimoto's thyroiditis) • Euthyroid
<Ocular – Other>	• [Specify - if not indicated above]

7.3.3 Efficacy Assessments

Planned time points for all efficacy assessments are provided in Table 4.

7.3.3.1 IDEEL-SB

Dry eye symptoms will be assessed using the IDEEL-SB questionnaire (see Appendix 17.2.1) at the Screening/Baseline visit (D1), before Systane Complete PF use, and at Visit 3 (and at unscheduled and at early exit visits, as necessary).

The IDEEL-SB (Version 1) symptom bother module consists of 20 questions that assess general dry eye symptoms a subject experiences. It should be administered prior to performing any other study testing procedure. The subject's response to each question will be entered on paper and scored to determine the eligibility of the subject to participate in the study.

Administration and Scoring

A paper copy of the IDEEL-SB module will be given to each subject for completion without assistance. All questions should be answered by the subject so please check the questionnaire before the subject leaves the study visit.

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 patient will be entered into the study source documents to determine eligibility at the Screening Visit.

[redacted]

7.3.4 Safety Assessments

Planned time points for all safety assessments are provided in Table 4.

7.3.4.1 Adverse Events

All AEs and SAEs will be collected at the time points specified in Table 4 from the time of informed consent completion until study participation is complete. Any preexisting medical conditions or signs/symptoms present in a subject prior to obtaining informed consent are not considered AEs in the study and should be recorded in the Medical History section of the eCRF. See Section 9.2 and 9.3 for further details.

7.3.4.2 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy assessments will be performed using the ISO11980 grading at the Screening/Baseline visit (D1) and at Visit 3 (and at unscheduled and early exit visits, as necessary).

A biomicroscopy examination of the cornea, adnexa and anterior segment of the eye will be performed, OD and OS, at the Screening/Baseline visit (D1) and at Visit 3 (and at unscheduled and early exit visits, as necessary), and recorded on eCRFs. Record both eyes for the same subject if both are noted to have such a finding.

If warranted, a short slit lamp video or slit lamp photograph should be recorded to demonstrate any abnormal findings or findings of interest during biomicroscopy (for example inferior arcuate staining). Record both eyes for the same subject if both are noted to have such a finding.

- Limbal hyperemia

Limbal hyperemia (redness) will be recorded on a 5-point scale as follows:

0 = None	No hyperemia
1 = Trace	Slight limbal hyperemia (mild segmented)
2 = Mild	Mild limbal hyperemia (mild circumcorneal)
3 = Moderate	Significant limbal hyperemia (marked segmented)
4 = Severe	Severe limbal hyperemia (marked circumcorneal)

- Bulbar Hyperemia

Bulbar conjunctival hyperemia (redness) will be recorded on a 5-point scale as follows:

0 = None	No hyperemia
1 = Trace	Slight regional hyperemia
2 = Mild	Diffuse hyperemia
3 = Moderate	Marked regional or diffuse hyperemia
4 = Severe	Diffuse episcleral or scleral hyperemia

- Corneal Epithelial Edema

Corneal epithelial edema should be classified according to the number of microcysts observed. The presence/absence of fluid-filled or debris-filled cysts should be documented.

0 = None	No microcysts; normal transparency
1 = Trace	1 to 20 microcysts; barely discernable local epithelial haziness
2 = Mild	21 to 50 microcysts; faint but definite localized or generalized haziness
3 = Moderate	51 to 100 microcysts; significant localized or generalized haziness
4 = Severe	> 100 microcysts; definite widespread epithelial cloudiness giving a dull glass appearance to the cornea or numerous coalescing bullae

- Corneal Staining
    - Corneal Staining Set Up

All corneal staining observations should be carried out using a blue excitation light to full intensity and magnification at 16x in conjunction with a yellow barrier filter in the observation system (approximate beam width 10 mm and height 8 mm).

Apply one drop of fresh, non-preserved, sterile saline to the tip of a Sodium Fluorescein (NaFl) impregnated strip. Allow saline to drip off the strip (i.e., without a shaking motion).

Ask the subject to look up and nasally. Gently retract the lower lid and touch the strip to the inferior temporal bulbar conjunctiva, approximately 5 mm or more from the limbus, for 1 to 2 seconds, so that 1 to 2 mm of the flat side of the strip makes contact with the ocular surface. Withdraw the strip and release the lower lid.

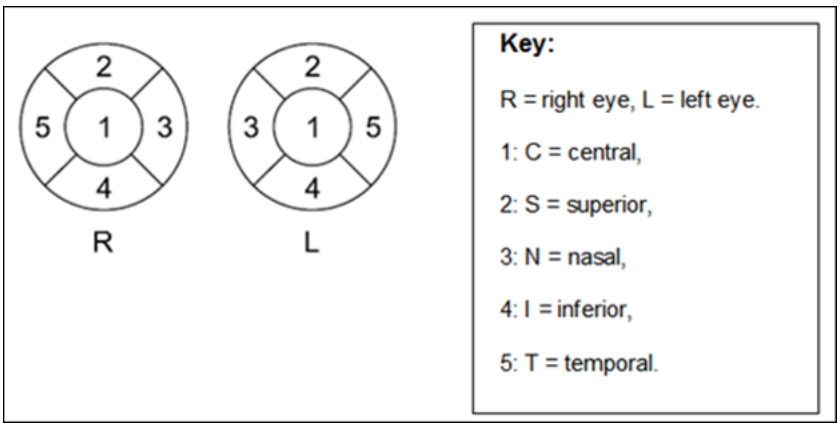
- Corneal Staining - Standard Assessment

Record grade according to the following scale:

0 = None	No staining
1 = Trace	Minimal superficial staining or punctate staining a) Dimpling, discrete dot staining, or b) Trace superficial lens insertion marks or foreign body tracks
2 = Mild	Regional or diffuse punctate staining a) Central or generalized, or b) Peripheral including 3 to 9 o'clock staining, or c) Foreign body tracks
3 = Moderate	Dense coalescent staining up to 2 mm in diameter a) Corneal abrasion b) Foreign body track
4 = Severe	Dense coalescent staining greater than 2 mm in diameter

The location of staining observed should be recorded in source documentation only, as indicated in Figure 3:

Figure 3. Corneal Regions for Recording Location



Recurrent erosion and corneal ulceration should be recorded under "Other findings."

Inferior arcuate staining should be recorded under "Other findings."

- Conjunctival Staining

Conjunctival staining should be assessed immediately after corneal staining. Therefore, an additional application of NaFl is not required. However, if needed in order to make a sound judgment, one more application can be made following the instructions given in the section above and using a new NaFl strip. All conjunctival staining observations should be carried out using a blue excitation light in conjunction with a yellow barrier filter in the observation system after NaFl instillation.

Conjunctival staining will be assessed on a 5-point scale:

0 = None	No staining
1 = Trace	Minimal regional staining
2 = Mild	Regional or diffuse punctate staining
3 = Moderate	Significant dense coalescent staining
4 = Severe	Severe dense geographical staining

- Palpebral Conjunctival Observations

The severity of the maximal palpebral conjunctival response will be recorded on a 5-point scale as follows:

0 = None	Uniform satin appearance of the conjunctiva
1 = Trace	Slight conjunctival injection without texture
2 = Mild	Mild or scattered papillae/follicles less than 1 mm in diameter
3 = Moderate	Significant papillae/follicles less than 1 mm in diameter, and/or marked conjunctival injection Staining of the top of one papilla
4 = Severe	Localized or generalized papillae/follicles 1 mm or more in diameter Staining of the top of more than one papilla

- Other Findings

Record any other finding(s) and use the following scale to grade severity:

0 = None	No other significant biomicroscopic findings
1 = Trace	Minimal findings
2 = Mild	Mild findings
3 = Moderate	Significant findings
4 = Severe	Severe findings

Note: If there are multiple other findings, on the eCRF for "Other" record the grade of the most severe in the "Result" field and record all findings (along with their individual grades) in the "If Other, Specify" field.

7.3.4.3 BCVA

BCVA will be assessed per standard practice at the Screening/Baseline visit (D1) and at Visit 3 (and at unscheduled and early exit visits, as necessary).

7.3.4.4 Device Deficiencies

Device deficiencies will be collected at the time points specified in Table 4.

7.4 Follow-Up Procedures and Therapy Transitions

In this study, there are no specific follow-up procedures or therapy transitions required. Following study completion, subjects will return to their previous care provider.

Alcon products associated with device deficiencies and/or product-related AEs should be returned when possible. Product returns must include the complaint number, which will be provided by study Sponsor after the case is entered in the study Sponsor's Global Product Complaint Management System (GPCMS).

Return any recoverable Alcon Product associated with a product-related AE (adverse device effect [ADE], serious adverse device effect [SADE]) or device deficiency to the Sponsor. Include the SAE/ADE or device deficiency eCRF in the return package. Maintain a copy of shipment tracking information and all documents submitted with the product.

7.5 Study Timetable / Schedule of Study Assessments

The schedule of study assessments is provided in Table 4.

Table 4. Schedule of Study Assessments

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	X			
Demographics	X			
Targeted medical history	X			
Targeted concomitant medications	X			
IDEEL-SB questionnaire	X		X	(X)
[redacted]	[redacted]			
Inclusion/Exclusion	X			
Changes in concomitant medications		X	X	X
BCVA	X		X	(X)
[redacted]	[redacted]		[redacted]	[redacted]
Biomicroscopy (include corneal staining)	X		X	(X)
AEs	X	X	X	X
Device deficiencies	X	X	X	X
Exit form	(X)		X	X
Telephone follow-up for compliance check		X		

AE: adverse event; BCVA: best corrected visual acuity; [redacted]; IDEEL-SB: Impact of Dry Eye on Everyday Life - Symptom Bother
(X) assessment performed as necessary
[a] On Day 1: before Systane Complete PF first dose, immediately after first dose, and 8 hours after first dose (prior to administering evening dose of Systane Complete PF)

7.6 Deviations from the Clinical Protocol

When a deviation from the protocol is necessary for an individual subject, the Investigator must contact the Sponsor (or its acting representative) prior to the deviation (unless the deviation is safety related). The subject may continue in the study by mutual agreement of the Sponsor and the Investigator. A description of the deviation from the protocol and justification must be recorded on the Protocol Deviation Form.

Deviations occurring without prior approval must be assessed by the Investigator and reviewed by the Sponsor. Subject continuation must be indicated on the Protocol Deviation Form. A description of the deviation from the protocol and justification must be recorded on the Protocol Deviation Form. Unintended deviations from the protocol must be recorded on a Protocol Deviation Form within 24 hours of the identification of the deviation. The Sponsor, or Sponsor's representative must be notified.

7.7 Clinical Study Termination

The study Sponsor reserves the right to suspend or close the investigational site or suspend or terminate the study in its entirety at any time.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
    - Discontinuation of further study treatment development
- For site termination:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator
    - Total number of subjects included earlier than expected

If the clinical study is prematurely terminated or suspended by the study Sponsor:

- The study Sponsor (or its acting representative) shall:
    - Immediately notify the Investigator(s) and subsequently provide instructions for study termination.

- Inform the Investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.

- The Investigator shall:
  - Promptly notify the IRB/IEC of the termination or suspension and of the reasons.
  - Provide subjects with recommendations for poststudy treatment options as needed.

7.8 Subject Compensation

Where permitted by the IRB/IEC, study subjects will be compensated for participation.

8 DATA COLLECTION AND ANALYSIS

8.1 Subject Populations for Analysis

Two analysis data sets will be defined:

- The Full Analysis Set (FAS) will include all subjects/eyes exposed to at least one dose of Systane Complete PF. The Full Analysis Set will serve as the primary analysis set for all effectiveness and safety analyses.
- The Per Protocol (PP) population is a subset of the FAS and will exclude subjects with major protocol deviations. The PP population will be a supportive set for effectiveness analyses, as necessary.

8.2 Statistical Methods

This section is a summary of the planned statistical analyses. A Statistical Analysis Plan will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section.

Statistical analyses will be presented overall and by DED groups (aqueous deficient dry eye, evaporative dry eye, mixed dry eye).

There is no statistical hypothesis for the endpoints in this study. Appropriate descriptive statistics will be computed and presented for all categorical and continuous endpoints.

- For categorical variables, the number and percentage of subjects/eyes within each category of interest will be presented.
- For continuous variables, the number of subjects/eyes with non-missing data, mean, standard deviation, range, median, minimum, and maximum will be presented.
- There will be no imputation for missing data.

All visual acuity results will be presented in logarithm of the minimum angle of resolution (logMAR) scale after applying appropriate transformations/conversions.

8.3 Interim Analyses

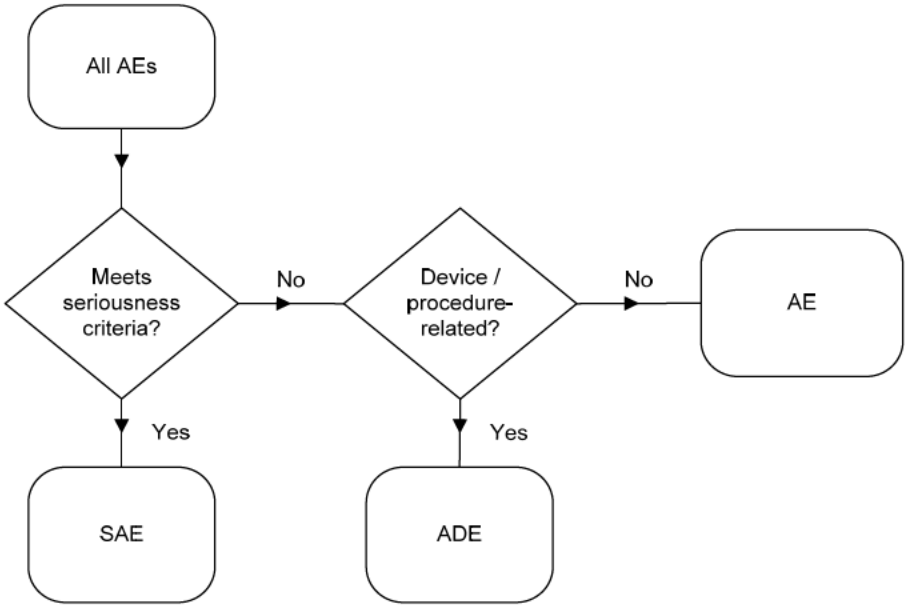
This section is not applicable.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

9.1 General Information

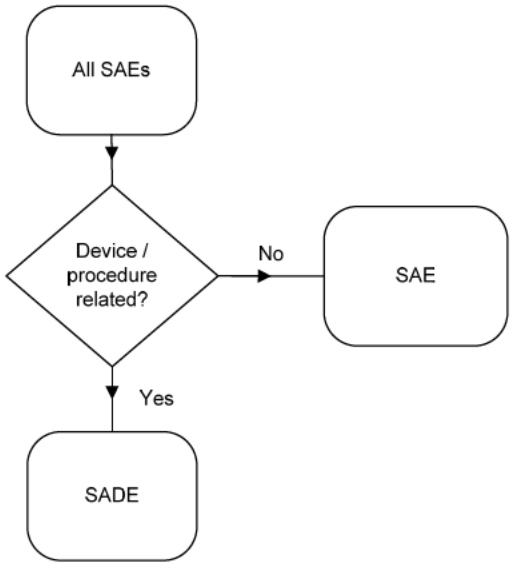
An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the study device. Refer to the Glossary of Terms (Section 17.1) and figures below for categories of AEs and SAEs.

Figure 4. Categorization of All AEs



ADE: adverse device effect; AE: adverse event; SAE: serious adverse event

Figure 5. Categorization of All SAEs



SADE: serious adverse device effect; SAE: serious adverse event

Device Deficiencies

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. A device deficiency may or may not be associated with patient harm (i.e., ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The Investigator should determine the applicable category listed in the Device Deficiency eCRF for the identified or suspect device deficiency and report any patient harm separately. Examples of device deficiencies include the following:

- Failure to meet product specifications
- Unsealed device packaging
- Suspected product contamination

9.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions shown below and report as applicable:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take because of a new health issue or worsening of an existing health issue since your last study visit?"

In addition, changes in any protocol-specific parameters and/or questionnaires evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant, in the opinion of the Investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

9.3 Procedures for Recording and Reporting

AEs are collected from the time of informed consent completion and throughout the duration of the study. Any preexisting medical conditions or signs/symptoms present in a subject prior to obtaining informed consent are not considered AEs in the study and should be recorded in the Medical History section of the eCRF.

For each recorded event, the ADEs and SAEs documentation must include: date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the Investigator must document all device deficiencies reported or observed with the study device on the Device Deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the study Sponsor immediately as follows:

- All SAEs must be reported immediately (within 24 hours) of the Investigator or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days of the Investigator or site's awareness.
- A printed copy of the completed SAE and ADE and/or Device Deficiency eCRF must be included with product returns.
- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- Any changes to concomitant medications must be documented on the appropriate eCRFs.
- All relevant information from Discharge Summary, Autopsy Report, Certificate of Death etc., if applicable, must be documented in the narrative section of the SAE and ADE eCRF.

Note: Should the EDC system become non-operational, the site must notify the Sponsor designee (ICON Clinical Research SAE Hotline) at +1-888-723-9952. The reported information must be entered into the EDC system once it becomes operational.

Study Sponsor representatives may be contacted for any protocol-related question and their contact information is provided in the Project Team Contact List included in the Investigator Site File.

Further, depending upon the nature of the AE or device deficiency being reported, the Study Sponsor (or designee) may request copies of applicable portions of the subject's medical records. The Investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or IRB/IEC.

Intensity and Causality Assessments

Where appropriate, the Investigator must assess the intensity (severity) of the AE based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild: An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.

Moderate: An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.

Severe: An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the Investigator must assess the causality (Related or Not Related to the study treatment). An assessment of causality will also be performed by study Sponsor utilizing the same definitions, as shown below:

Causality

Related An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the study treatment has not been demonstrated, but there is a reasonable possibility that the AE was caused by the study treatment.

Not Related An AE classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the AE).

The study Sponsor will assess the AEs and may upgrade the Investigator's assessment of seriousness and/or causality. The study Sponsor will notify the Investigator of any AEs that is upgraded from nonserious to serious or from unrelated to related.

9.4 Return Product Analysis

Alcon study products associated with device deficiencies and/or product-related AEs should be returned and must include the Complaint number, which will be provided by study Sponsor after the case is entered in the study Sponsor's GPCMS.

9.5 Follow-up of Subjects with Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study.

The Investigator should provide the study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the study treatment. For AEs that are unresolved/ ongoing at time of subject exit from study, any additional information received at follow-up should be documented in the eCRFs up to study completion (i.e., database lock).

All complaints received after this time period will be considered and processed as spontaneous (following the post-market vigilance procedures) and should be communicated to the study treatment's manufacturer as per local requirements.

9.6 Pregnancy in the Clinical Study

Women of childbearing potential or women who become pregnant during the course of the study are not excluded from participation. Pregnancy should be included in the Pregnancy eCRF should a woman become pregnant during the data collection period or if a woman becomes pregnant during the study. Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case–by-case basis if information is available in medical records.

9.7 Anticipated Clinical Benefits and Risks

9.7.1 Known Potential Risks

Systane Complete Preservative-Free may cause mild eye burning or irritation, itching or redness of the eyes, watery eyes, blurred vision, or unpleasant taste in the mouth. There may be a rare possibility of an allergic reaction, which could be severe.

Systane Complete must be stopped in the event of eye pain, changes in vision, continued redness or irritation of the eye, or if condition worsens or persists for more than 72 hours.

9.7.2 Known Potential Benefits

Previous clinical studies showed that Systane Complete is effective for the temporary relief of burning and irritation due to dryness of the eye, for the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun, for use as a protectant against further irritation or to relieve dryness of the eye, and for use as a lubricant to prevent further irritation or to relieve dryness of the eye.

10 DATA HANDLING AND RECORD KEEPING

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the HIPAA of 1996, the General Data Protection Regulation (EU 2016/679), and applicable national and local regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the eCRF shall match the *Source Data* recorded on the *Source Documents*.

10.3 Case Report Forms

The study eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, or if the item is not applicable to the individual case, please reference the eCRF Completion Guides on how to enter in the eCRF.

An eCRF will be completed for each subject enrolled into the clinical study. The Investigator will review, approve and sign/date each completed eCRF; the Investigator's signature serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered on the eCRF are complete, accurate and authentic.

The electronic data capture method utilized will be in compliance with the Food and Drug Administration (FDA)'s electronic records and electronic signatures regulations at 21 CFR Part 11.

10.4 Clinical Reports

The Investigator is responsible for the preparation and submission of annual progress reports as required by local IRBs/IECs. The Sponsor is responsible for the preparation of the final Clinical Study Report, which will be submitted to appropriate IRBs/IECs by the Investigator.

A Coordinating Investigator may be identified by the study Sponsor to review and endorse the final study report. In cases where a Coordinating Investigator is engaged, the study Sponsor will select the Coordinating Investigator based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role.

10.5 Records Retention

The Sponsor shall keep relevant clinical records for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period.

The Investigator shall maintain relevant clinical records for 10 years. Investigators will notify the Sponsor at least 60 days prior to any destruction of records at the address listed below:

Alcon Research LLC
6201 South Freeway
Fort Worth, Texas 76134

Or via email to:

Record.Retention@Alcon.com

11 STUDY MONITORING, AUDITING, AND INSPECTING

This study will be monitored according to GCP guidelines. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.1 Study Monitoring Plan

The Sponsor will ensure that the study is adequately monitored and in accordance with the Study Clinical Monitoring Plan.

Monitors will be appropriately trained, with scientific and/or clinical knowledge needed to monitor the clinical study adequately. Monitors are required to be thoroughly familiar with the protocol, the informed consent documentation provided to subjects, Sponsor and Sponsor's Designee Standard Operating Procedures (SOPs), GCPs, and the applicable regulatory requirement(s).

Site visits will be conducted by an authorized Sponsor representative to inspect study data, subjects' medical records, and case report forms (CRFs) in accordance with current GCPs and the respective local and national government regulations and guidelines (if applicable). The study Investigator and the investigating site will permit authorized clinical research personnel and clinical monitors from Sponsor and/or designee(s) to review completed CRFs, IRB/IEC decisions, and Investigator, clinical site records, and facilities relevant to this study at regular intervals throughout the study per the monitoring plan. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. Monitoring may be performed with in-person visits or remotely, when applicable.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will review training records to ensure all study staff are trained on the study protocol and use of the study device. If the monitor discovers that an Investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/IEC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, the Investigator's participation in the investigation may be terminated. Independent monitoring of the clinical study for clinical protocol compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff.

11.2 Quality Assurance Procedures

Quality control and quality assurance is the responsibility of the Investigator and designated study staff. Sponsor clinical representatives will provide training and support to ensure that data quality is optimal (accurate, valid, reliable, complete and reported in a timely manner).

This study shall adhere to US FDA standards, European Union (EU) Regulations, Health Canada Regulations as well as other applicable local standards of conduct regarding quality assurance. All parts of the US CFR applicable to clinical studies, including 21 CFR Parts 50 and 56, and 46 CFR 164, European Union Medical Device Regulation [EU 2017/745], General Data Protection Regulation [EU 2016/679] and Medical Device Regulations SOR/98-282 and Food and Drugs Act must be followed.

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor or Sponsor designee may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at the study sites and during data management to assure that data are adequate and well documented.

The Investigator shall promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

The Study Sponsor or designee will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Study Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Study Sponsor with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

11.3 Auditing and Inspection

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the Sponsor, government regulatory bodies, and institutional compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices.

12 PROTOCOL AMENDMENTS AFTER STUDY INITIATION

Should changes in the study plan or protocol become necessary in the course of the clinical trial, those specific changes will be discussed and agreed upon by the Sponsor, its acting representative if appropriate, Investigator, and appropriate IRB/IEC approval obtained before the changes are implemented. All changes must be documented as protocol amendments.

13 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of GCP, applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB/IEC, in agreement with local legal regulations, for formal approval of the study conduct. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study.

The study Sponsor will select Principal Investigators (PIs) that are qualified by education, training, and experience to assume responsibility for the proper conduct of this clinical trial. For this study, the PI and sub-Investigators must be health care professionals appropriately trained and/or licensed.

The Investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The Investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. Deviations from this protocol, regulatory requirements and/or GCP must be recorded and reported to the Sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol must be approved by an IRB/IEC. The Investigator must provide documentation of the IRB/IEC approval to the Study Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any). The IRB/IEC must be provided with a copy of the Package Insert/Directions for Use, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the study, the Investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the Investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject or legal representative, as applicable, and the process shall be documented before any data are being collected for this study. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or their delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information regarding the purpose,

procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the study device and the study, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent (filed in subject's medical records) and must provide a duplicate of the signed copy to each subject according to local regulations.

14 STUDY FINANCES

14.1 Funding Source

This study is financed by Alcon Research LLC. The Sponsor will secure a human clinical trial insurance certificate according to applicable country regulations, when required.

14.2 Conflicts of Interest

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under US FDA 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Potential conflicts of interest will be subject to the processes and procedures of the institutions where the potential conflict exists.

15 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study Sponsor. Any Investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

At the conclusion of the trial, a multi-center manuscript may be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the publication of the multi-center results. Any and all exceptions to this rule require the prior written approval of the Sponsor. Investigators may publish study results, provided Sponsor receives a copy of any proposed oral presentation or written publication at least 60 days in advance of submission for publication for review. Sponsor

has the right to comment on the appropriateness of the data analysis and presentation and have that comment reflected in the presentation. Investigator will meet with Sponsor prior to submission for publication for the purpose of making good faith efforts to discuss and resolve any issues or disagreement. Upon Sponsor's request, Investigator shall remove from any such oral presentation or written publication any material provided to Investigator by Sponsor or any confidential material. In addition, if requested in writing by Sponsor, Investigator will withhold such publication an additional 60 days to allow for filing a patent application or taking such other measures as Sponsor deems appropriate to establish and preserve its proprietary rights.

The clinical trial will be registered in a publicly accessible clinical trial registry in accordance with the Sponsor's choice, and/or applicable national regulatory requirements. Clinical trial results will be posted within the registry in accordance with registry requirements.

16 REFERENCES

16.1 References Applicable to All Clinical Studies

- ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice
- ISO11980: Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations

16.2 References Applicable to Clinical Studies Conducted in the United States

- 21 CFR 11: Electronic Records; Electronic Signatures
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosures by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 42 CFR 11: Clinical Trials Registration and Results Information Submission
- 45 CFR 164: Security and Privacy

16.3 Cited References

1. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017;15(3):334-365.
2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–283.
3. Friedman NJ. Impact of dry eye disease and treatment on quality of life. Curr Opin Ophthalmol. 2010;21(4):310–316.

4. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II Report Executive Summary. Ocul Surf. 2017; 15:802-812.

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17 APPENDICES AND ATTACHMENTS

17.1 Glossary of Terms

Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device or comparator. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse.*
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or comparator and whether anticipated or unanticipated. *Note: For subjects, this definition includes events related to the investigational medical device, comparator, or the procedures involved. For users or other persons, this definition is restricted to the use of investigational medical device or comparator.*
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling related to the investigational medical device or the comparator.*
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan (CIP), or Investigator's brochure (IB).
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Product Complaint	Written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: a) A life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, i.e., it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* *b)* Any potentially sight-threatening event or permanent impairment to a body structure or a body function including chronic diseases. c) In-patient hospitalization or prolonged hospitalization. d) A medical or surgical intervention to prevent a) or b).

	e) Any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, congenital abnormality or birth defect including physical or mental impairment. *Note: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event*
Serious Public Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death, serious deterioration in state of health or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. *Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals*.
Use Error	User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. *Note:* *a) Use error includes the inability of the user to complete a task.* *b) Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.* *c) Users might be aware or unaware that a use error has occurred.* *d) An unexpected physiological response of the patient is not by itself considered a use error.* *e) A malfunction of a medical device that causes an unexpected result is not considered a use error.*

17.2 Patient Questionnaires

17.2.1 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	☐	☐	☐	☐	☐

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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.

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