a Novartis company

Short Title

Clear Care® Plus for Presbyopic Contact Lens Wearers

Long Title

Clinical Study of Clear Care® Plus for Presbyopic Contact Lens Wearers

Protocol Number:	LCS739-P001 / NCT02965833
Study Phase:	N/A
Sponsor Name and Address:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Investigational Product:	Clear Care® Plus Cleaning & Disinfecting Solution (CCP)
US IND# / EudraCT	N/A
Indication Studied:	Cleaning and disinfection of soft contact lenses
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Sponsor.
Principal Investigator:	
	Signature Date
Name:	
Address:	

1 SYNOPSIS

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number:** LCS739-P001
Investigational Product:	CLEAR CARE Plus Cleaning & Disinfecting Solution (CCP)	**Study Phase:** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☒ N/A
Protocol Title:	Clinical Study of CLEAR CARE Plus for Presbyopic Contact Lens Wearers	
Investigator(s)/ No. of Sites:	Approximately 9 sites	
Center Location(s)/	United States	
No. of Subjects	**Duration of Treatment:**	
Required: 110 completed Planned: approximately 120 randomized (approximately 8 to 20 subjects per site)	30 ± 3 days per period each product (up to 66 days total)	

Study Population: Current presbyopic soft contact lens wearers (2-week/monthly replacement modalities only) with symptoms of contact lens induced dryness and habitually using a non-HydraGlyde® containing multi-purpose solution (MPS) (target at least 50% using a Biotrue® formulation habitually).

Objective(s): The overall objective of this study is to demonstrate the benefit of CCP compared to non-HYDRAGLYDE multipurpose contact lens solutions in presbyopes currently wearing soft contact lenses and experiencing symptoms of dryness.

The primary objective is to demonstrate superiority of CCP when compared to the subject's habitual multipurpose solution (HMPS) in reducing symptoms of contact lens induced dryness after 30 days of use, based on responses to the CLDEQ-8 (abbreviated Contact Lens Dry Eye Questionnaire).

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[redacted]

[redacted]

Methodology: This is a prospective, randomized, crossover (2-treatment, 2-period), stratified (BIOTRUE and other HMPS), observer-masked, and quasi-subject-masked study.

Treatments:

Investigational Product: CCP

Route of Administration: Remove and place each lens into the appropriately marked L/R domed lens holder, and thoroughly rinse with CCP for 5 seconds. Fill the CCP lens cup to the fill line with CCP and place the lens holder in the lens cup. Tighten the cap

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		(finger tight) on the CCP lens cup and store lenses for at least 6 hours. Refer to MOP for detailed instructions for use in the package insert.
	Duration of Treatment:	The subject will wear their habitual lens brand (following manufacturer recommended replacement) on a daily wear basis for 30 ± 3 days using CCP daily to care for their lenses.
	Dosage:	Up to 32 cleaning and disinfecting cycles will be used for the study.
	Control Article:	Habitual Multi-purpose Solution
	Route of Administration:	Refer to MOP for detailed instructions for use in the package inserts.
	Duration of Treatment:	The subject will wear their habitual lens brand (following manufacturer recommended replacement) on a daily wear basis for 30 ± 3 days using their habitual solution daily to care for their lenses.
	Dosage:	Up to 32 cleaning and disinfection cycles will be used for the study.

Subject Selection: **Inclusion Criteria:**

1. Age 45-65 (both inclusive) and must sign the informed consent.
2. Current adapted two-week/monthly replacement soft contact lens wearers (at least 2 months) with symptoms of contact lens induced dryness as defined by the Symptomatology (Eligibility) Pre-screening questionnaire.

   Note: Subject may be wearing multifocal contact lenses or single vision contact lenses prescribed for monovision or for distance only.
3. Requires a near spectacle ADD of +0.50 or greater.
4. Best corrected visual acuity (BCVA) to 20/30 or better in each

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eye at distance at Visit 1.

5. Willing to wear lenses for a minimum of 5 days per week 6 hours per day, and attend all study visits.
6. Currently (at least 2 months) using a non- HYDRAGLYDE containing multi-purpose solution to care for their lenses [Opti-Free® Puremoist® Multi-Purpose Contact Lens Solution (OFPM) contains HYDRAGLYDE and is thus not allowed].
7. Uses digital devices (eg, smart phone, tablet, laptop computer, or desktop computer) for 20 consecutive minutes at least twice a week and willing to continue the same pattern for the duration of the study as assessed at Pre-screening.

Exclusion Criteria:

1. Extended wear (sleeps in lenses one or more nights per week).
2. Any anterior segment infection, inflammation, disease, or abnormality that contraindicates contact lens wear as determined by the Investigator.
3. Any use of systemic medications or ocular medications for which contact lens wear could be contraindicated, as determined by the Investigator, including use of any topical ocular medications that would require instillation during contact lens wear.
4. Monocular subjects (only 1 eye with functional vision) or subjects fit with only 1 lens.
5. A known sensitivity to any ingredients in CCP.
6. Biomicroscopy findings observed during the Visit 1 slit-lamp examination that are moderate (grade 3) or worse in either eye.
7. Prior refractive surgery (eg, laser assisted in situ keratomileusis [LASIK] and photorefractive keratectomy [PRK]).
8. History of herpetic keratitis, ocular surgery, or irregular cornea.

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9. A pathological dry eye that precludes contact lens wear.
10. Use of mechanical eyelid therapy or eyelid scrubs within 14 days before Visit 1 and not willing to discontinue during the study.
11. Enrollment of the Investigator or his/her staff, family members of the Investigator, family members of the Investigator's staff, or individuals living in the households of these individuals.
12. Enrollment of more than 1 member of the same household in the study.
13. Participation in any clinical study within 30 days of Visit 1.
14. Subjects who are currently using or have not discontinued Restasis®, Xiidra® or a topical steroid within the past 7 days.

Assessments:

- CL-induced dryness symptoms as measured by CLDEQ-8
- Symptomatology pre-screening questionnaire
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Biomicroscopy
- Snellen visual acuity
- AEs and device deficiencies

Statistical Methods: **Planned Analysis**:

Three analysis sets will be defined: safety, full, and per protocol (PP). The safety analysis set will include all subjects/eyes exposed to any

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study lens care products evaluated in this study. The full analysis set (FAS) is the set of all randomized subjects who are exposed to any study lens care products. The PP analysis set is a subset of all randomized subjects and excludes those who meet the critical deviation criteria as specified in the Deviations and Evaluability Plan (DEP). The FAS will serve as the primary analysis set for all efficacy evaluations.

All data from evaluable subjects will be included in the efficacy analysis; no imputation for missing values will be performed.

Efficacy:

To address the primary efficacy objective, planned analyses are summarized below.

Endpoint	Comparison	Statistical Method
PRIMARY		
CLDEQ-8 (Day 30)	CCP vs HMPS Superiority	Mixed effect repeated measure model. Baseline score as a covariate.

[redacted]

[redacted]

[redacted]

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[redacted]

Safety:

Each safety variable will be summarized descriptively. AEs will be classified as treatment-emergent, based on treatment-specific exposure, or pre-treatment. Count and percentage will be provided by relationship to device, and separate tables will be generated for ocular and nonocular AEs. Counts and percentages in each grade category will be presented for each biomicroscopy parameter. Device deficiencies will also be tabulated. Supporting subject listings describing details of each safety variable will be provided. Listings describing details of AEs reported prior to usage of the study solutions will be presented separately from the safety analysis for the treatment-emergent AEs.

Sample Size Justification: Sample size calculations for the primary endpoint are summarized below (one-sided α=0.05).

Endpoint	Assumptions	Power	N
Primary			
CLDEQ-8	SD=10 (paired differences)	80% Detectable difference=3	36 per each of the 2 crossover sequences

[redacted]

1.1 Amendments

Amendment 1

Purpose of Amendment: To implement revisions based on the change in Exclusion Criteria

Rationale: To align with study specific requirements

Current Study Status: Study execution

Case Report Form Revision Required: ☐ Yes ☒ No

Informed Consent Modifications Required: ☐ Yes ☒ No

Applicable Investigators: ☒ All ☐ Selected (list below)

Itemized Changes:

Change	**Rationale**
Section 8.2: Exclusion Criteria number 14 **Change from:** Subjects who are currently using or have not discontinued RESTASIS within the past 7 days. **To** Subjects who are currently using or have not discontinued RESTASIS, XIIDRA or a topical steroid within the past 7 days.	To include range of concurrent products prohibited to use in the study.

1.2 Glossary of Terms for Safety

Adverse Event (AE)	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 investigational medical device (test article). *Note: For subjects, this definition includes events related to the test article, the control article, or the procedures involved. For users or other persons, this definition is restricted to events related to the test article.*
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (test article) or control article. *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 of the test article or control article.*
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 inadequate labeling.*
Malfunction	Failure of a medical device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of the device refers to the intended use for which the device is labeled or marketed.
Product Complaint	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.
Non-serious Adverse Event	Adverse event that does not meet the criteria for 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 that either resulted in: 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, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* Any potentially sight-threatening event or permanent impairment to a body structure or a body function. In-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* A medical or surgical intervention to prevent a) or b) Any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. Fetal distress, fetal death, or a congenital abnormality or birth defect. *Refer to Section 12 for additional SAEs.*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, eg, human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD).

Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

2 OVERVIEW OF STUDY PLAN

	Visit 1	**Visit 2**	**Visit 3**	**USV**
Procedure/Assessment	**Screening & Baseline Period 1/Day 1**	**Period 1 Day 30 ± 3 Follow-Up Period 2/Day 1**	**Period 2 Day 30 ± 3 Follow-Up /Exit**	**Unscheduled Visit**
Pre-Screening questionnaire (symptomatology, digital device use, and HMPS identification)[a]	X (before consent)			
Informed consent	X			
Collect demographics and activities	X			
Medical and lens/lens care history	X			
Concomitant medications/ changes in concomitant medications	X	X	X	X
Subjective (manifest) refraction[a]	X	(X)	(X)	(X)
BCVA[a]	X	(X)	(X)	(X)
Inclusion/exclusion	X			
Randomization	X			
Dispense a new pair of habitual lenses and assign/dispense the study lens care solution per randomization. Educate on instructions for use.	X	X		(X)
Snellen VA with lenses	X[b]	X[b, d]	X[d]	(X)
[redacted]				
Biomicroscopy	X	X	X	X
CLDEQ-8 Questionnaire	X[c]	X	X	
[redacted]				

	Visit 1	Visit 2	Visit 3	USV
Procedure/Assessment	**Screening & Baseline Period 1/Day 1**	**Period 1 Day 30 ± 3 Follow-Up Period 2/Day 1**	**Period 2 Day 30 ± 3 Follow-Up /Exit**	**Unscheduled Visit**
[redacted]				
Assess AEs	X[e]	X	X	
Assess device deficiencies	X	X	X	X
Document wear time compliance (days, hours) and lens care compliance[a]		X	X	(X)
Exit form	(X)	(X)	X	(X)

[a]Source only
[b]With new lenses being dispensed at the visit
[c]Based on habitual regimen
[d]With lenses worn for the study period.
[e]AEs are collected from the time of informed consent.
(X)= as needed.
AEs=adverse events, BCVA=best corrected visual acuity, CLDEQ-8=Contact Lens Dry Eye Questionnaire-8, HMPS=Habitual multi-purpose solution, IRB=Institutional review board, USV=unscheduled visit, VA=visual acuity

3 ABBREVIATIONS

Abbreviation	Definition
ADD	Added magnifying power
ADE	Adverse device effect
AE	Adverse event
BCVA	Best corrected visual acuity
B&L	Bausch & Lomb
°C	Degrees Celsius
CCP	Clear Care Plus Cleaning & Disinfecting Solution
CI	Confidence interval
CJD	Creutzfeldt-Jacob Disease
CL	Confidence limit or contact lens
CLC	Contact lens care
CLDEQ-8	Contact Lens Dry Eye Questionnaire-8
CSM	Clinical site monitor
DEP	Deviations and evaluability plan
eCRF	Electronic case report form
EDC	Electronic data capture
EOBO	Ethylene oxide and butylene oxide
EudraCT	European Clinical Trials Database
°F	Degrees Fahrenheit
FAS	Full analysis set
FDA	US Food and Drug Administration
fl. oz.	Fluid ounce
GCP	Good Clinical Practice
GPCMS	Global Product Complaint Management System
HIV	Human immunodeficiency virus
HMPS	Habitual multi-purpose solution
IEC	Independent ethics committee
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IND	Investigational new drug
IRB	Institutional review board
L/R	Left/right
LASIK	Laser assisted in situ keratomileusis
MedDRA®	Medical Dictionary for Regulatory Activities
mL	Milliliter
MOP	Manual of procedures
MPS	Multi-purpose solution
N/A	Not applicable
n	Number
OFPM	Opti-Free Puremoist Multi-Purpose Contact Lens Solution
PP	Per protocol

Abbreviation	Definition
PRK	Photorefractive keratectomy
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SDV	Source data verification
TDOC	Technical document
US	United States of America
USV	Unscheduled visit
VA	Visual acuity

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5 INTRODUCTION

5.1 Study Rationale and Background

Silicone hydrogel contact lenses pose unique challenges for contact lens care solutions; the solutions must efficiently remove tear lipid deposits and keep the hydrophobic silicone material wettable at the surface. CLEAR CARE, a hydrogen peroxide based lens care system, has already proven to be biocompatible with silicone hydrogel lenses (Andrasko 2008, Carnt 2007). Recently, the US Food and Drug Administration (FDA) cleared a new hydrogen peroxide disinfecting solution, CLEAR CARE Plus cleaning & disinfecting solution (CCP) with an added substantive wetting agent, EOBO-21–polyoxyethylene-polyoxybutylene. Both solutions are designed to result in very low residual peroxide levels after 6 hours neutralization.

CCP is a preservative-free, aqueous solution containing hydrogen peroxide 3%, phosphonic acid (stabiliser), sodium chloride (0.79%), phosphate (buffer system), and PLURONIC 17R4 (a cleaning agent / surfactant) and HYDRAGLYDE Moisture Matrix (EOBO-21 – polyoxyethylene-polyoxybutylene). CCP has been shown to keep lenses wettable for longer and to improve comfortable lens wearing time in symptomatic lens wearers (Muya 2015, TDOC-0051197).

The purpose of this study is to demonstrate the benefit of CCP cleaning & disinfecting solution in presbyopic contact lens wearers with symptoms of dryness as compared to their HMPS (≥50% using a BIOTRUE formulation). The primary objective is to demonstrate superiority of CCP cleaning & disinfecting solution compared to the subject's HMPS in reducing symptoms of contact lens-related dryness after 30 days of use, based on responses to the CLDEQ-8 (abbreviated Contact Lens Dry Eye Questionnaire).

This market support study is designed to provide continued reasonable assurance of the effectiveness of CCP in a specified population of symptomatic presbyopic soft contact lens wearers that fall under the indication of the product. The effectiveness endpoint was identified based on the findings from another post-approval study in a general population of symptomatic soft contact lens wearers who were habitually using multi-purpose solutions to care for their lenses. Preserved multi-purpose solutions are the most popular types of disinfection systems in the marketplace, therefore are a reasonable control to the test solution in this study which is a preservative-free hydrogen peroxide based disinfecting system including a wetting agent that may benefit some soft lens wearers.

5.2 Known and Potential Risks

Contraindications, warnings, important safety information, and adverse reactions for CCP cleaning & disinfecting solution with HYDRAGLYDE may be found in product labeling.

The risks with contact lens wear are increased with a pre-existing or active ocular infection or inflammation, improper lens fit, and noncompliance with regimen. It is essential that contact lens care (CLC) users follow directions and all labeling instructions for proper use of their contact lenses and lens care products, including the lens case. Subjects who are noncompliant and fail to follow the instructions for cleaning, storage, and disinfection of their contact lenses could experience an eye infection or injury. A corneal ulcer could develop rapidly and lead to loss of vision. Contact lens wearers unfamiliar with a hydrogen peroxide solution could inadvertently use the peroxide solution as a lubricating/rewetting drop or rinse their contact lenses prior to insertion, resulting in chemical burn due to the unneutralized peroxide solution. Additionally, using the wrong lens cup, overfilling the lens cup with peroxide solution or disinfecting the lenses for less than the specified time can result in incomplete neutralization of the peroxide solution. In such cases, adverse ocular effects such as discomfort, burning, stinging, pain, inflammation or irritation as well as chemical burn or irritation to the fingers may occur. These adverse events are usually temporary, and users should be instructed to immediately flush the eyes or fingers with saline or water should this occur. Overall, the potential risks associated with use of the subject's HMPS and CCP cleaning & disinfecting solution are similar when used as indicated.

5.3 Potential Benefits

CCP cleaning & disinfecting solution is indicated for use in simultaneous cleaning, daily protein removal, disinfection, and storing of soft (hydrophilic) contact lenses (including silicone hydrogel lenses) and rigid gas permeable (fluoro silicone acrylate and silicone acrylate) contact lenses, as recommended by an eye care professional. Unlike multi-purpose solutions, CCP is preservative-free and when used as directed, may benefit lens wearers who are sensitive to preservatives. CCP when used as indicated may also improve the wettability of the contact lens surface. Based on known product information, in the opinion of Alcon, the benefits gained by the use of the formulation outweigh the risks associated with its use.

6 ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Before clinical study initiation, this protocol, the informed consent form, MOP, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB). The Investigator must provide documentation of the IEC/IRB approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, MOP, all applicable recruiting materials, written information for subject, and subject compensation programs. The IEC/IRB must be provided with a copy of the Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator will notify the IEC/IRB about the study's completion. The IEC/IRB also will be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent will be obtained from every subject (and/or legal representative, as applicable) prior to the initiation of any Screening or other study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will 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 copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and will 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 investigational product, 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 will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also will 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 and must provide a duplicate copy to each subject.

7 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study may be required by the IRB to sign the approved, revised informed consent form.

This is the first amended version of protocol LCS739-P001.

8 SUBJECT POPULATION

Approximately 120 subjects (approximately 8 to 20 subjects per site) are to be randomized at approximately 9 United States (US) sites to achieve approximately 110 subjects completed. An advertisement may be used to aid recruitment. The advertisement will be submitted to the IEC/IRB for approval. The IRB approved Pre-screening questionnaire will be provided before taking the consent.

The enrollment for the study is planned for 6 weeks. The expected duration of subject participation in the study (3 scheduled visits) is 30±3 days per study period (up to 66 days total). The complete inclusion and exclusion criteria are presented in Section 8.1 and Section 8.2.

8.1 Inclusion Criteria

1. Age 45-65 (both inclusive) and must sign the informed consent.
2. Current adapted two-week/monthly replacement soft contact lens wearers (at least 2 months) with symptoms of contact lens induced dryness as defined by the Symptomatology (Eligibility) Pre-screening questionnaire.

   Note: Subject may be wearing multifocal contact lenses or single vision contact lenses prescribed for monovision or for distance only.
3. Requires a near spectacle ADD of +0.50 or greater.
4. Best corrected visual acuity (BCVA) to 20/30 or better in each eye at distance at Visit 1.
5. Willing to wear lenses for a minimum of 5 days per week 6 hours per day, and attend all study visits.
6. Currently (at least 2 months) using a non- HYDRAGLYDE containing multi-purpose solution to care for their lenses (OFPM contains HYDRAGLYDE and is thus not allowed).
7. Uses digital devices (eg, smart phone, tablet, laptop computer, or desktop computer) for 20 consecutive minutes at least twice a week and willing to continue the same pattern for the duration of the study as assessed at Pre-screening.

8.2 Exclusion Criteria

1. Extended wear (sleeps in lenses one or more nights per week).

2. Any anterior segment infection, inflammation, disease, or abnormality that contraindicates contact lens wear as determined by the Investigator.
3. Any use of systemic medications or ocular medications for which contact lens wear could be contraindicated, as determined by the Investigator, including use of any topical ocular medications that would require instillation during contact lens wear.
4. Monocular subjects (only 1 eye with functional vision) or subjects fit with only 1 lens.
5. A known sensitivity to any ingredients in CCP.
6. Biomicroscopy findings observed during the Visit 1 slit-lamp examination that are moderate (grade 3) or worse in either eye.
7. Prior refractive surgery (eg, LASIK and PRK).
8. History of herpetic keratitis, ocular surgery, or irregular cornea.
9. A pathological dry eye that precludes contact lens wear.
10. Use of mechanical eyelid therapy or eyelid scrubs within 14 days before Visit 1 and not willing to discontinue during the study.
11. Enrollment of the Investigator or his/her staff, family members of the Investigator, family members of the Investigator's staff, or individuals living in the households of these individuals.
12. Enrollment of more than 1 member of the same household in the study.
13. Participation in any clinical study within 30 days of Visit 1.
14. Subjects who are currently using or have not discontinued RESTASIS, XIIDRA or a topical steroid within the past 7 days.

9 TREATMENTS ADMINISTERED

Upon completing Pre-screening Questionnaire and satisfying the relevant pre-screening criteria, subjects will sign informed consent and then be considered enrolled into the study. A subject ID number will be assigned to enrolled subjects by entering the subject into the electronic data capture (EDC) system. Subjects eligible after Screening at Visit 1 will be randomized (1:1) to receive either CCP or HMPS to care for their lenses in Period 1 of the study. For Period 2, the contact lens solution that was not allocated for use in Period 1 will be dispensed. The randomization will be stratified by HMPS (BIOTRUE vs. Other MPS). Throughout the study, designated unmasked site personnel at the investigational site will be responsible for the accounting of all study products and will ensure that the study products are not used in any unauthorized manner.

9.1 Identity of Study Treatments

Investigational Product: CCP
Control Product: HMPS

CCP will be supplied in sterile 12 fl. oz. (355 mL) filled bottles with investigational labelling. A new lens case will be supplied with each bottle.

Table 9-1 Study Treatments

Properties	CCP (Test product)	HMPS (Control product)
Administration	Subjects will use CCP to store and disinfect their contact lenses as instructed by the study team member(s) dispensing the solution and according to the instructions for use.	Subjects will use their HMPS to store and disinfect their contact lenses as instructed by the study team member(s) dispensing the solution and according to the instructions for use.
Duration of Treatment	The subject will wear their habitual lens brand (following manufacturer recommended replacement) on a daily wear modality for 30 ±3 days using CCP daily to care for their lenses.	The subject will wear their habitual lens brand (following manufacturer recommended replacement) on a daily wear modality for 30 ±3 days using their habitual solution daily to care for their lenses.

Properties	CCP (Test product)	HMPS (Control product)
Quantity/Dosage	Up to 32 cleaning and disinfecting cycles will be used for the study.	Up to 32 cleaning and disinfection cycles will be used for the study.
Supply	CCP will be supplied in sterile 10 fl. oz. (355 mL) filled bottles with investigational labelling. A new lens case will be supplied with each bottle. The product is manufactured by Alcon Laboratories in Fort Worth, Texas. The study kit will contain one bottle of the test article (bottle will be re-labeled), and a lens cup that contains platinum disk for neutralization of the solution. Marketed sterile saline (Bausch & Lomb Sensitive Eyes® Plus in commercial packaging) will be provided separate from the kit by the unmasked study coordinator to each subject to use for rinsing lenses and cases as needed. Note: Habitual rewetting drops may be used as needed throughout the study. Rewetting drop use frequency will be collected at baseline and follow-up.	HMPS will either be: 1) Purchased by the subject and reimbursed. The unmasked site personnel must confirm a new bottle of the HMPS identified at pre-screening is purchased by the subject and used for the assigned study period. 2) Purchased by the site according to the HMPS identified at pre-screening and dispensed to the subject for use during the assigned study period. HMPS will be dispensed/used in commercial packaging. The manufacturer information for each product can be found in the package insert. Note: Habitual rewetting drops may be used as needed throughout the study. Rewetting drop use frequency will be collected at baseline and follow-up.

CCP will be provided in the commercial bottle but will be re-labeled. Included on the investigational labels for the randomized product will be the kit number, protocol number, fill

volume, storage conditions, the indicator "Disinfecting Solution" and a statement that the product is for investigational use only. CCP should be stored at room temperature (15°C to 30°C / 59°F to 86°F) or below. Additionally the following warnings will be included on the investigational label: "IMPORTANT: Misuse will result in burning and stinging. Use only lens case provided. Do not remove lenses from the lens case for at least 6 hours. The solution needs time to neutralize. Never rinse lens with product prior to insertion. Red snap cap means product is not for direct use on eye.

More information on the CCP or HMPS can be found in the Product Labeling. Refer to the MOP for product labels.

The new label will be sufficient to mask the CCP, thus maintaining the subject masking to brand. A designated unmasked staff member (other than the Investigator) at the site will be assigned to dispense the sealed test kit and the HMPS to ensure Investigator masking. Unmasked site personnel cannot conduct study specific procedures.

9.2 Usage

Subjects will use the study contact lens solutions according to the instructions provided by the unmasked coordinator who dispenses the study lens solutions. Each treatment period (Period 1 and Period 2) will last for 30 (±3) days. In addition to dispensing the randomized study contact lens solutions at the respective visit, subjects will be dispensed and fitted with a new pair of their habitual silicone hydrogel contact lenses (including an extra pair of lenses for 2 week replacement between visits, if required for use in each treatment period). The lens dispensations and all planned and unplanned lens replacements must be documented in the source.

9.3 Accountability Procedures

Designated unmasked site personnel will dispense the study contact lens solutions (re-labeled CCP and the site/subject purchased commercially labeled HMPS) in accordance with their assigned subject ID number and the randomization treatment order allocated to them. The identity of the test product will not be revealed to the subject and the order of use of the test and control products will not be revealed to the Investigator. It will not be possible to maintain full subject masking due to the nature of the cleansing devices, but the brand name will be masked for the test solution. During the study, the investigational site must maintain records of study treatment dispensation and collection by the unmasked personnel for each subject. This record must be made available to the designated study monitors for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies

between the observed disposition and the written account must be recorded along with a detailed explanation. Study contact lens cleaning devices associated with a device deficiency or with any product-related AEs must be returned to the Sponsor or manufacturer (for comparator/reference product). Refer to Section 12 for additional information on the reporting of device deficiencies or product-related AEs.

At the conclusion of the study, the Investigator will be responsible for returning all used and unused study supplies unless otherwise instructed by the Sponsor.

Upon receipt of the test products (CCP test solution kits) from Alcon, the, unmasked coordinator will conduct an inventory. During the study, the unmasked coordinator must maintain records of study treatment dispensation and collection for each subject including study solutions (test CCP or purchased control HMPS). This record must be made available to the study monitor for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. At the conclusion of the study, the Investigator will be responsible for returning all used and unused study supplies unless otherwise instructed by the Sponsor.

9.4 Subject Confidentiality and Methods Used to Minimize Bias

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the clinical study, the Sponsor will collect a copy of the enrollment log without any identifying subject information. All documents submitted to the Sponsor will identify the subjects exclusively by subject ID and demographic information. No other personally identifying information should be transmitted to the Sponsor.

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of end points, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the test article(s) by the Investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

This study is Investigator-masked and subject quasi-masked (masked to test solution brand only), with subjects randomized to the order in which they will use CCP and their HMPS for

30±3 days each. The Investigator will not be aware of the specific treatment being administered and the subject will not be aware of the brand of the test solution. Alcon study personnel will be masked, with the exception of the following: Study monitor, Lead CSM, and person responsible for generating the randomization schedule. This level of masking will be maintained throughout the conduct of the study. Subjects will be assigned treatment order based on the randomization schedule; it will be blocked to ensure a balance of study treatment allocations within investigational sites. The randomization scheme will be generated and maintained by the Sponsor. In the event of a medical emergency where the knowledge of subject treatment is required, an individual Investigator will have the ability to unmask the treatment sequence assignment for a specific subject.

10 STUDY PROCEDURES

10.1 Outline of Study

Prior to informed consent and scheduling the Screening visit, subjects will be given the Pre-screening Questionnaire (Symptomatology Questionnaire, Digital Device Use assessment and HMPS Identification Tool). These may be administered via a combination of phone, email, or in person (note: the HMPS Identification Tool is visual). Once the subject completes the questionnaire and the replies indicate the subject to be eligible to proceed then inform consent must be obtained from the subject before any procedure specified by this protocol is initiated, including Screening procedures at Visit 1. The original signed informed consent must be maintained with the subject's file whether they pass or fail screening. A copy of the signed informed consent form will be provided to the subject. Data from the Pre-screening Questionnaire will not be entered into to the electronic case report forms (eCRFs) but will stay in the subject file as source documents for monitoring of both randomized subjects and screen failures. Those who pass pre-screening and sign informed consent may attend the Screening visit (Section 10.2.1).

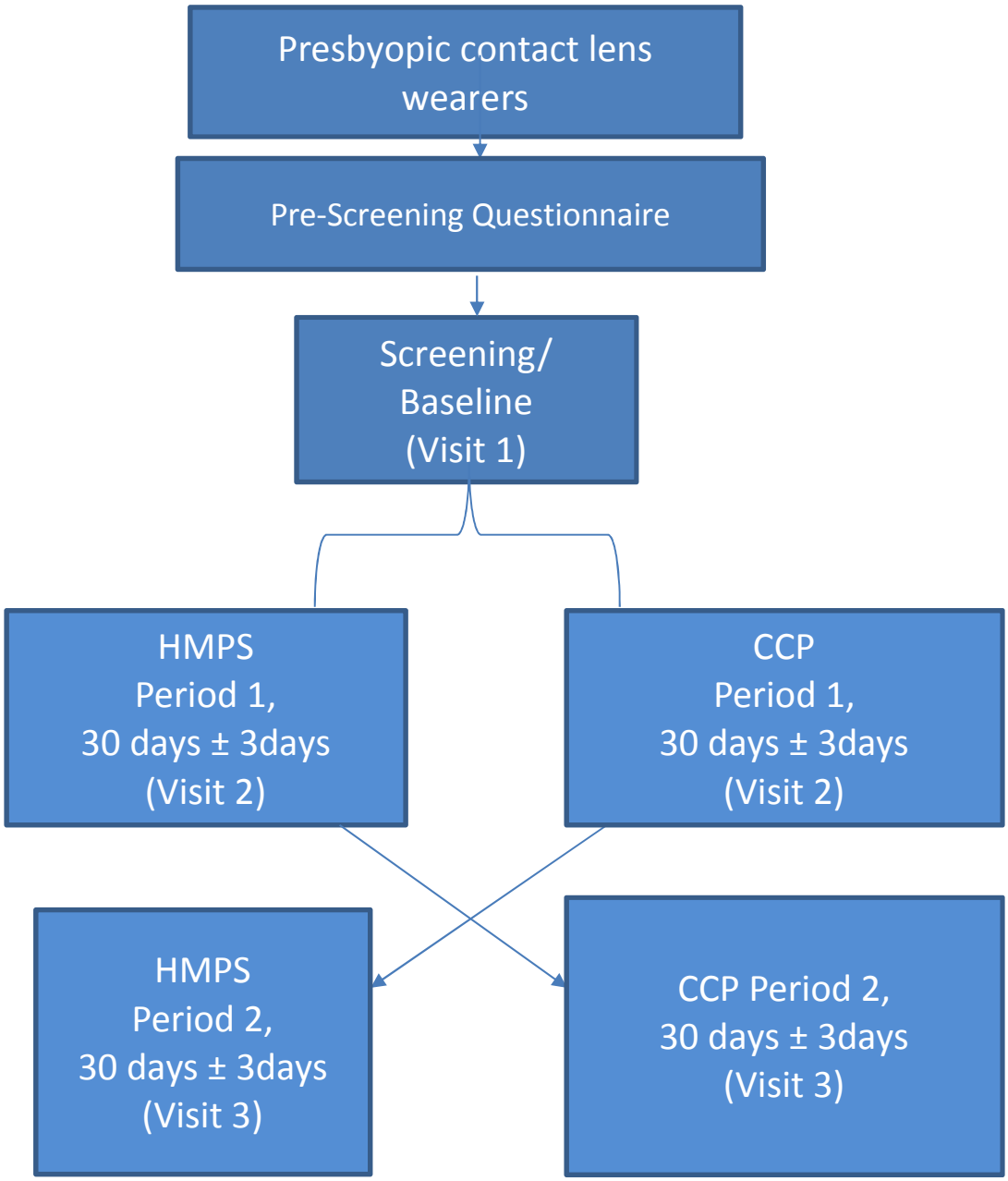
Subjects who are scheduled to attend the Screening Visit must have a new bottle of the HMPS identified during pre-screening ready for possible dispensing at the end of the Screening visit after randomization. This can be accomplished in two ways for the study:

1) The subject purchases a new bottle of the HMPS and brings it to the Screening visit. In this case the subject will be reimbursed for their purchase. The unmasked coordinator must confirm the solution purchased was the HMPS identified during pre-screening and that it is not expired. If HMPS is randomized to be used for Period 2, the site will maintain the purchased HMPS at the site for the subject until Period 2;

2) The site purchases the subject's HMPS and dispenses to the subject according to the randomization schedule.

Adverse events (AEs)/serious adverse events (SAEs) and device deficiencies will be assessed and reported at all scheduled and unscheduled study visits for each subject from the time of informed consent.

Figure 10–1 Diagram of Study Design



10.2 Visits and Examinations

10.2.1 VISIT 1– SCREENING/BASELINE & PERIOD 1/DAY 1 VISIT

1.	If the pre-screened eligible subject was asked to purchase a new bottle of their own HMPS, then the site should ensure the HMPS purchased matches the HMPS identified at pre-screening and is not expired. If this does not occur, the Screening visit should be rescheduled.
2	Have the subject read, sign, and date the IEC/IRB approved informed consent document. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document. Provide a photocopy of the signed document to the subject and place the original signed document in the subject's chart.
3	Enter the subject into the EDC system to obtain a subject ID. Note: A subject ID is needed for all subjects who sign an informed consent form (including screen failures).
4	Obtain demographic information, medical and lens/lens care history (including confirmed HMPS), typical activities performed while being active, concomitant medications/ changes in concomitant medications including information on all medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications.
5	Have subject complete Subjective Questionnaires based on habitual lenses and care system (CLDEQ-8, [redacted]
6	Remove lenses and perform subjective (manifest) refraction. For details refer to MOP.
7	Perform BCVA assessment. For details refer to MOP.
8	Perform biomicroscopy assessments using slit-lamp examination scales. For details refer to MOP. Review inclusion/exclusion criteria to determine if the subject qualifies to be randomized into the study.
9	Only for subjects qualifying to be included in the study, confirm randomization by entering details of eligibility into the EDC system and obtain study solution assignment for each period.

10	Dispense a new pair of habitual lenses and perform Snellen VA with new lenses being dispensed at the visit. For details refer to MOP. For two-week replacement lens wearers, provide the subject an extra pair of study lenses for replacement at two weeks. Contact the subject at approximately 15 ± 1 days of the study period to remind the subject to replace their lenses and document date of replacement in the source.
11	Unmasked coordinator to assign/dispense the study lens care solution for Period 1 per randomization scheme. 1) HMPS purchased by the subject or provided by the site –or- 2) Investigational Masked CCP Kit with Kit # and B&L Sensitive Eyes Saline. Educate on instructions for use and emphasize for the first-time hydrogen peroxide CLC users the warnings and use of the correct lens case with the product.
12	Assess and record any adverse events (AEs) that are reported or observed from the time of informed consent (see Section 12).
13	Record any device deficiencies that are observed or reported.
14	Schedule Visit 2 (Period 1 Follow-up) to take place on Day 30 ± 3 days (scheduled 29 (±3) days after Visit 1. Provide subject with Visit 2 reminder instructions: • The subject should bring the used lens case for the study period, along with their dispensed study solution used during the study period.

10.2.2 VISIT 2 – PERIOD 1/Day 30 & PERIOD 2/DAY 1

1	Document wear time compliance (days, hours) and lens care compliance. Collect used study lens care product(s) from the subject.
2	Obtain information on any changes in medical health and/or the use of concomitant medications since Visit 1.
3	Have subject complete the Subjective Questionnaire based on lenses worn and study solution used during the 30 day study period (CLDEQ-8, [redacted]
4	Conduct Snellen VA with worn lenses. For details refer to MOP.
5	[redacted]

6	Remove lenses and perform biomicroscopy assessments using slit-lamp examination scales. For details and order of staining procedures, refer to MOP. Perform subjective (manifest) refraction assessment and BCVA assessment (as needed). For details refer to MOP.
7	Assess and record AEs that are observed or reported (See Section 12).
8	Record any device deficiencies that are observed or reported.
9	Dispense a new pair of habitual lenses and perform Snellen VA with new lenses being dispensed at the visit. For details refer to MOP. For two-week replacement lens wearers, provide the subject an extra pair of study lenses for replacement at two weeks. Contact the subject at approximately 15±1 days of the study period to remind the subject to replace their lenses and document date of replacement in the source.
10	Unmasked coordinator to assign/dispense the study lens care solution for Period 2 per randomization scheme. 1) HMPS purchased by the subject or provided by the site –or- 2) Investigational Masked CCP Kit with Kit # and B&L Sensitive Eyes Saline. Educate on instructions for use and emphasize for the first-time hydrogen peroxide CLC users the warnings and use of the correct lens case with the product.
11	Schedule Visit 3 (Period 2 Follow-up) to take place on Day 30 ±3 days (scheduled 29 (±3) days after Visit 2. Provide subject with Visit 3 reminder instructions: • The subject should bring the used lens case for the study period, along with the dispensed study solutions used during the study period.

10.2.3 VISIT 3 – Period 2/ DAY 30 /EXIT

1	Document wear time compliance (days, hours) and lens care compliance. Collect used study lens care product(s) from the subject.
2	Obtain information on any changes in medical health and/or the use of concomitant medications since Visit 2.
3	Have subject complete the Subjective Questionnaire based on lenses worn and test solution used during the 30 day study period (CLDEQ-8, [redacted]

4	Conduct Snellen VA with worn lenses. For details refer to MOP.
5	[redacted]
6	Remove lenses and perform biomicroscopy assessments using slit-lamp examination scales. For details and order of staining procedures, refer to MOP.
7	Perform subjective (manifest) refraction assessment and BCVA assessment (as needed). For details refer to MOP.
8	Assess and record AEs that are observed or reported (see Section 12).
9	Record any device deficiencies that are observed or reported.
10	Exit the subject from the study.

10.3 Unscheduled Visits

Any visit that occurs between the regularly scheduled visits must be documented in the unscheduled visit pages of the eCRF. During all unscheduled visits, the following procedures should be conducted:

- Document wear time compliance (days, hours) and lens care compliance.
- Obtain information on any changes in medical health and/or the use of concomitant medications.
- Perform Snellen VA with lenses (as needed).
- Perform subjective (manifest) refraction (as needed).
- Perform BCVA assessment (as needed).
- Perform biomicroscopy.
- Record any AEs or device deficiencies that are observed or reported.
- Replace lenses and dispense additional study lens care solution for the study period if needed (as needed). Record all unplanned lens replacement dates in the source.
- Exit the subject from the study (if subject is discontinuing at the unscheduled visit).

If the subject is discontinuing at the unscheduled visit, the Early Exit visit eCRF should be completed rather than the eCRF form for an Unscheduled visit.

10.4 Discontinued Subjects and Screen Failures

Discontinued subjects are those who withdraw or are withdrawn from the study after being randomized. Subjects may discontinue from the study at any time for any reason. Subjects

may also be discontinued from the study at any time if, in the opinion of the Investigator, their continued participation poses a risk to their health. Discontinued subjects will not be replaced (ie, their subject numbers will not be re-assigned/re-used).

If a subject is identified not to fulfill the eligibility criteria for study inclusion during the Screening visit (Visit 1), the subject will be screen failed and will not participate any further in the study. The EDC system will be updated to confirm the subject is a screen failure. The Investigator will explain to the subject the reason(s) why eligibility was not met and provide appropriate information/treatment, if required. The Exit form will be completed for all discontinued subjects and screen failures.

Should a subject exhibit any clinically relevant signs, symptoms, or other clinical observations that possibly could be associated with suspected sensitivity or intolerance to one of the study treatments, the Investigator must document those observations on an AE Form. Observations must also be reported for occurrences not associated with any study treatment (see Section 12.3, Procedures for Recording and Reporting AEs and SAEs).

Any subject who exits early from the study should undergo all procedures outlined at Visit 3/Exit. Additionally, the Exit Form must be completed and the reason for discontinuation must be identified and captured in EDC.

Finally, to ensure the safety of all subjects who discontinue early, Investigators should assess each subject and, if necessary, advise them of any therapies and/or medical procedures that might be needed to maintain their health.

10.5 Clinical Study Termination

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities of the termination/ suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons. The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause. Reasons for the closure of an investigational site or termination of a study may include:

- Successful completion of the study
- The study's enrollment goals are met
- The Investigator fails to comply with the protocol or GCP guidelines
- Safety concerns

- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the Investigator

The Investigator also may terminate the study at his/her site for reasonable cause. If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s) by telephone and subsequently will provide written confirmation of and instructions for study termination.

11 ANALYSIS PLAN

Continuous variables will be summarized for the observed values using the number of observations, mean, SD, median, minimum and maximum, as well as CIs or CLs where applicable. Categorical variables will be summarized with counts and percentages from each category. Any deviations to this analysis plan will be updated during the course of the study as part of a protocol amendment or will be detailed in the clinical study report.

11.1 Subject Evaluability

The final subject evaluability will be determined prior to breaking the code for masked lens care sequence assignment and locking the database.

11.2 Analysis Data Sets

11.2.1 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. The safety analysis set will include all subjects/eyes exposed to the newly dispensed habitual lenses for the study disinfected with at least one study lens product evaluated in this study. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual lens care product exposed.

11.2.2 Full Analysis Set

The FAS is the set of all randomized subjects who are exposed to at least one of the study lens care products as defined for the Safety Analysis Set.

11.2.3 Per Protocol Analysis Set

The PP analysis set is a subset of all randomized subjects and excludes all data/subjects which have met any of the critical deviation criteria identified in the DEP.

11.3 Demographic and Baseline Characteristics

Demographic information (age, sex, ethnicity, and race) will be summarized on the safety, full, and PP analysis sets. Baseline characteristics on habitual lens and lens care information as well as activities, CLDEQ-8, [redacted], [redacted] will be summarized on the full and PP analysis sets. Due to the crossover design, demographic and baseline data will be presented by lens care sequence group and overall.

11.4 Efficacy Analyses

This study defines one primary endpoint [redacted] All efficacy evaluations will use the FAS as the primary analysis set. [redacted]

For all planned inferential analyses, alternative models/methods may be considered if convergence cannot be achieved.

11.4.1 Primary Efficacy

The primary objective of this study is to demonstrate superiority of CCP when compared to habitual lens care product in reducing dryness symptomatology as measured by CLDEQ-8.

The corresponding endpoint is the score (range 0 to 37) from CLDEQ-8, obtained by adding the numerical responses to each of the 8 items, collected at the Day 30 follow-up, for each product (Visit 2 and Visit 3).

11.4.1.1 Statistical Hypotheses

The null and alternative hypotheses are formulated as follows:

$$H_0: \mu_{(CCP)} - \mu_{(HMPS)} \geq 0$$

$$H_a: \mu_{(CCP)} - \mu_{(HMPS)} < 0$$

where $\mu_{(CCP)}$ and $\mu_{(HMPS)}$ denote the mean CLDEQ-8 score for CCP and HMPS, respectively, at the Day 30 follow-up.

11.4.1.2 Analysis Methods

A mixed effect repeated measures model will be fit to test these hypotheses, including terms for lens care solution, period, sequence group, and baseline CLDEQ-8 as fixed effects and subject as a random effect. Lens care difference (CCP minus HMPS) and the corresponding one-sided 95% upper confidence limit will be provided.

Descriptive summary statistics will also be presented for the subgroup of habitual BIOTRUE formulation users.

11.4.2 Secondary Efficacy

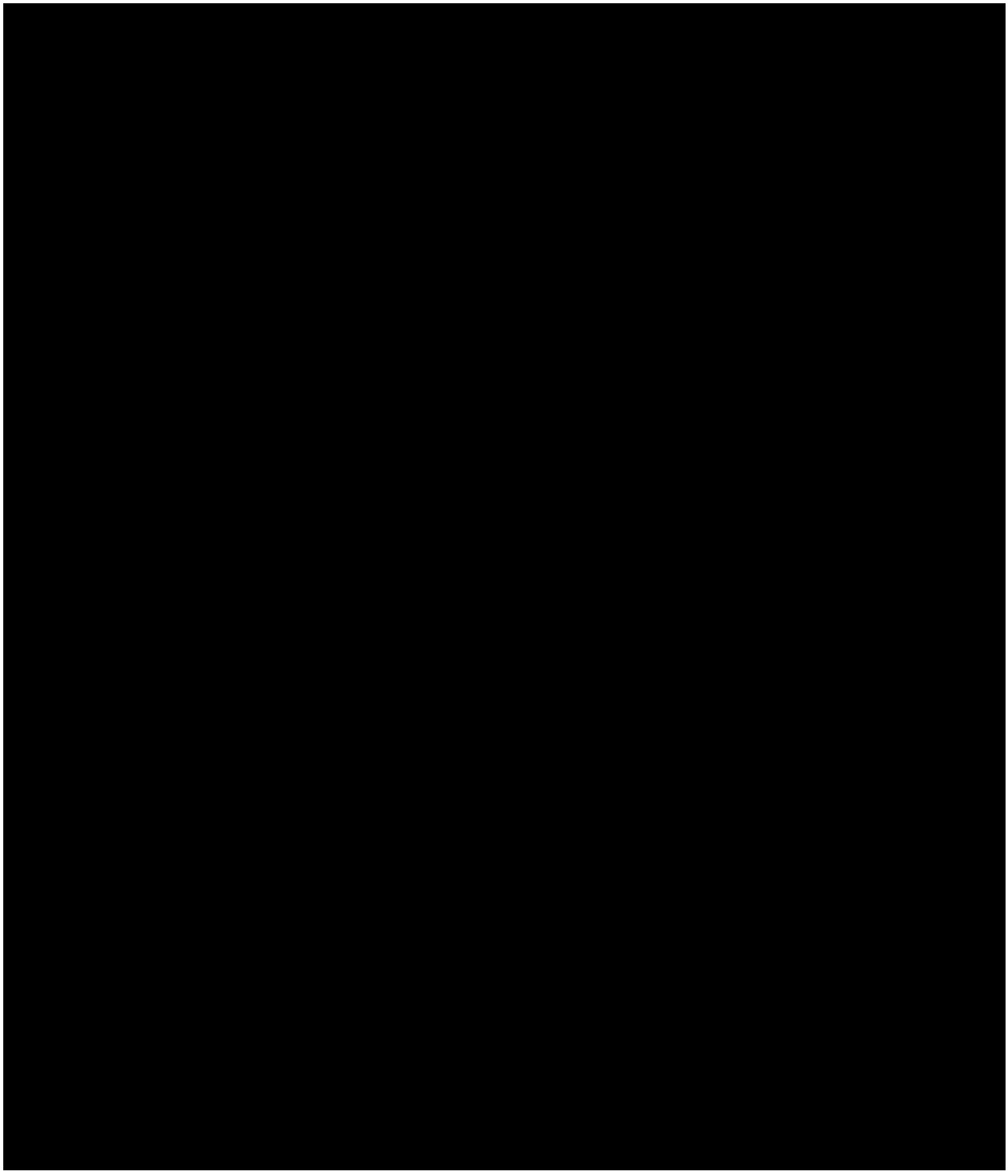
No secondary efficacy objective is defined for this study.

11.4.2.1 Statistical Hypotheses

Not applicable.

11.4.2.2 Analysis Methods

Not applicable.



11.5 Handling of Missing Data

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out for the efficacy analysis.

11.7 Safety Analysis

The safety endpoints for this study are AEs, biomicroscopy findings, and device deficiencies.

Descriptive summaries (counts and percentages) for ocular and nonocular AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms. In addition to an overall presentation of AEs, reports will be generated for serious AEs. AEs leading to study discontinuation will be identified. Individual subject listings will be provided, as necessary.

Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to study lens care solutions.

Each biomicroscopy parameter will be tabulated by its grade. For each biomicroscopy parameter, counts and percentages of eyes that experience an increase of ≥ 2 grades from baseline to any subsequent visit will be presented. Baseline is defined as Visit 1. A supportive listing will be generated which will include all biomicroscopy data from the affected visit for those eyes experiencing the increase of ≥ 2 grades, with the following variables: lens care solution, Investigator, subject, age, sex, visit, eye, parameter, baseline value, and value at the visit.

Two listings (prior to exposure of investigational products, and treatment-emergent) of device deficiencies, as recorded on the device deficiency Form, will be provided. Additionally, each device deficiencies category will be tabulated.

No inferential testing will be done for safety analysis.

11.8 Health Economics

Not applicable

11.9 Interim Analyses

Not applicable

11.10 Sample Size Justification

Sample size calculation for each of the relevant efficacy endpoints is described below.

Primary Efficacy:

Sample size calculation for the primary efficacy hypothesis on decrease in symptomatology is based on published data (Chalmers 2012). With an assumed SD for paired differences of 10, a sample size of 36/sequence will provide 80% power to detect a difference of 3 at one-sided α=0.05.

12 ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 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 investigational medical device (test article). Refer to the Glossary of Terms for categories of AEs and SAEs.

Figure 12–1 Categorization of All Adverse Events

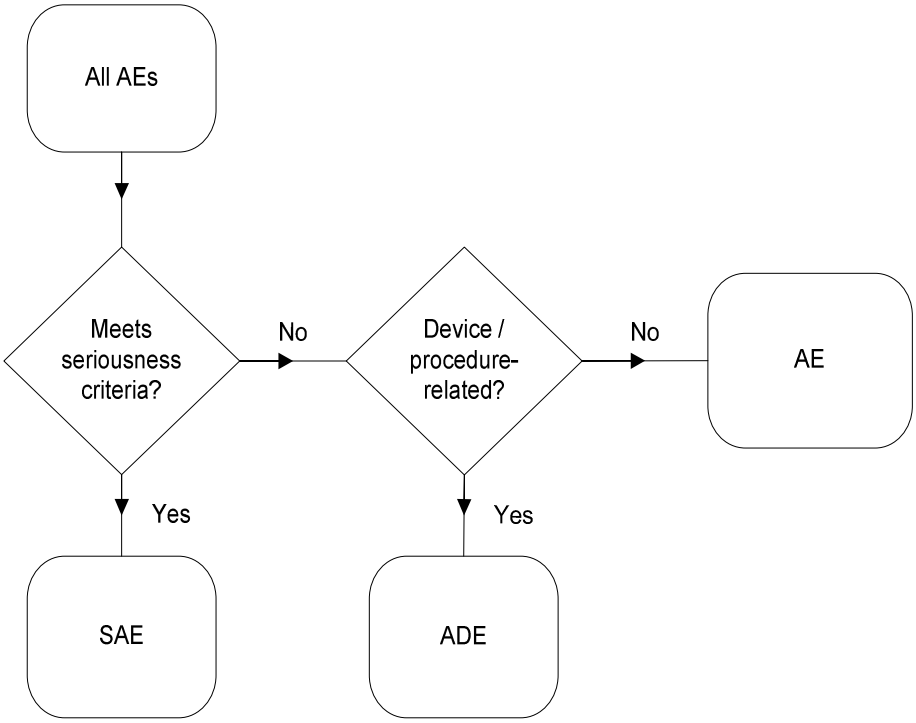
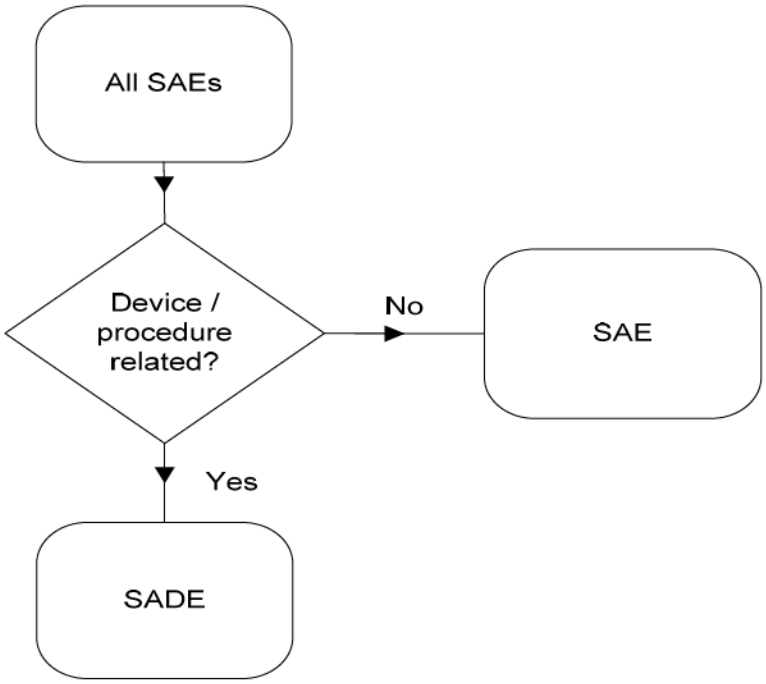


Figure 12-2 Categorization of All Serious Adverse Events



Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and should be reported appropriately as delineated in Section 12.3.

Device Deficiencies

A device deficiency may or may not be associated with subject harm (ie, ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The Investigator should determine the applicable category for the identified or suspect device deficiency and report any subject harm separately.

- Failure to meet product specifications
- Solution cloudy
- Packaging deficit (eg, mislabeled product, tampered seal, leaking bottle/container)
- Suspect product contamination
- Lack of performance

12.2 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:

- "Have you had any health problems since your last study Visit?"
- "Have there been any changes in the medicines you take since your last study Visit?"

Changes in any protocol-specific parameters and 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.

12.3 Procedures for Recording and Reporting

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

- All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days of the Investigator's or site's awareness.
- A printed copy of the completed ***Serious Adverse Event and Adverse Device Effect*** 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.
- Document any changes to concomitant medications on the appropriate eCRFs.
- Document all relevant information from Discharge Summary, Autopsy Report, Certificate of Death, etc, if applicable, in narrative section of the Adverse Device Effect (for related AEs) and Serious Adverse Event eCRF.

Note: Should the EDC system become non-operational, the site must complete the appropriate paper ***Serious Adverse Event and Adverse Device Effect*** and/or ***Device Deficiency*** Form. The completed form is faxed or emailed to the Study Sponsor at

[redacted] according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

Any AEs and device deficiencies for non-study marketed devices/products will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

Study Sponsor representatives may be contacted for any protocol-related question and their contact information is provided in the Manual of Procedures that accompanies this protocol.

Further, depending upon the nature of the AE or device deficiency being reported, the Study Sponsor 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.

12.4 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 medical device or study procedure). 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 medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.

Not Related — An AE classified as not related may either be definitely unrelated or simply unlikely to be related (ie, 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 are upgraded from non-serious to serious or from unrelated to related.

12.5 Return product analysis

Study Sponsor representatives and their contact information are provided in the Manual of Procedures that accompanies this protocol.

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

12.6 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study. If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate Study Sponsor representative prior to unmasking the information if there is sufficient time. Dependent upon the individual circumstances (ie, medical emergency), the code may be broken prior to contact with the Study Sponsor. The Study Sponsor must be informed of all cases in which the code was broken and of the circumstances involved. Additionally, the Study Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

12.7 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 device. 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 (ie, database lock).

All complaints received after this time period will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements.

The Investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

12.8 Pregnancy in the Clinical Trial

Pregnancy should be included in the Medical History section of the eCRF when 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.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the eCRFs exist and are accessible for verification by the site monitor. If electronic records are maintained, the method of verification must be determined in advance of starting the study. At a minimum, source documents should include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)
- Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- Trial medication accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of trial completion and reason for early discontinuation, if applicable
- Pre-screening Questionnaire Responses
- Manifest Refraction and BCVA (as needed)
- Compliance with study and study regimen
- Planned and unplanned lens replacement dates

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

Electronic CRFs (eCRFs) will be provided to the sites; only designated individuals may complete the eCRFs. The eCRFs will be submitted at regular intervals based upon the clinical trial visit schedule. It is expected that all data reported will have corresponding entries in the source documents and that the Principal Investigator will review the reported data and certify

that the eCRFs are accurate and complete. No subject identifiers should be recorded on the eCRFs beyond subject number, and demographic information.

Deviations from this protocol, regulatory requirements, and GCP must be recorded in the study records. An explanation of the deviation should be included, as applicable. In addition, corrective and preventive action should be identified, implemented, and documented within the study records.

13.2 Data Review and Clarifications

Targeted eCRF data will be reviewed against the subject's source data by the study monitors according to the SDV plan to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the eCRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are documented and are part of each subject's eCRFs.

13.3 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Sponsor and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is not subject to regulatory inspection and should be kept separately.

Additionally, the Investigator must keep study records and source documents until the Sponsor provides written approval for their destruction. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the **latest** marketing approval).

13.4 Clinical Trial Results

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Alcon, Inc. Alcon reserves the right of prior review of any publication or presentation of information related to the study. Alcon may use these data now and in the future for presentation or publication at Alcon's discretion or for submission to government regulatory agencies.

14 References

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15 APPENDIX

Not Applicable.