Alcon A Novartis Division

Short Title

Clinical comparison of silicone hydrogel monthly lenses

Long Title

One-month clinical comparison of silicone hydrogel monthly lenses in high lipid depositors

Protocol Number:	CLL541-P001/ NCT03169153
Study Phase:	Not applicable
Sponsor Name and Address:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Investigational Product:	AIR OPTIX® plus HydraGlyde (AOHG)
US IND#/EudraCT	Not applicable
Indication Studied:	Contact Lens Wear
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described study in compliance with Good Clinical Practice (GCP), ISO 14155: 2011 Clinical investigation of medical devices for human subjects, 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: CLL541-P001**
Investigational Product:	AIR OPTIX plus HydraGlyde (AOHG)	**Study Phase:** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☒ N/A - Post market
Active Ingredient:	N/A	
Protocol Title:	One-month clinical comparison of silicone hydrogel monthly lenses in high lipid depositors	
Investigator(s)/No. of Sites:	1	
Center Location(s)	United Kingdom	
No. of Subjects	Required: 70 completed (35/sequence) Planned: Approximately 78 randomized and approximately 140 screened/enrolled	
Duration of Treatment:	30 (+3) days per period	
Study Population:	Volunteer subjects at least 18 years of age who wear monthly replacement silicone hydrogel lens and are classified as high lipid depositors. Other eligibility criteria must also be met.	
Objectives:	**Primary Objective** The primary aim of the study is to confirm that a silicone hydrogel contact lens that attracts lower levels of total lipids *in vitro* (AOHG) also attracts lower levels of total lipids *in vivo* compared with a silicone hydrogel contact lens with high *in vitr*o lipid attraction (ACUVUE® VITA® (VITA)) in habitual high lipid depositor lens wearers. Therefore, the primary objective is to demonstrate superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.	

[redacted]

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[redacted]

Safety:

To collect and describe Biomicroscopy Findings, Adverse Events (AEs), and Device Deficiencies

Methodology: Single-site, prospective, randomized (lens sequence), double-masked crossover study

Treatments: **Investigational Product:** AOHG (Manufacturer: Alcon Laboratories, Inc.)
Lenses are *Conformité Européenne*

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(CE) marked and will be used as per their CE marking.

Route of Administration: The lenses will be dispensed by a trained unmasked study staff member so that neither the subject nor the Investigator will be able to see the lens label and hence, will remain masked to the identity of the lens.

The trained unmasked study staff member will not conduct any of the safety and effectiveness assessments after randomization, [redacted]

Subjects will use the lenses as instructed by the investigational site, according to the instructions for use.

Duration of Lens Wear: Subjects will wear the lenses bilaterally for a total duration of 30 (+ 3) days under a daily wear modality for the specific study period.

The lenses will be removed every night and cared for with the subject's habitual lens care solution.

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number: CLL541-P001**
	Dosage:	Lenses will be available in the following parameters: Material: Sphere lotrafilcon B (33% water) with plasma surface treatment Base curve: 8.6 millimeters (mm) Diameter: 14.2 mm Rx Range: +6.00 D to -8.00 D (0.25 D steps) and -8.50 D to -12.00 D and +6.50 D to +8.00 D (0.50 D steps)
	Control Product:	ACUVUE VITA (Manufacturer: Johnson and Johnson Vision Care, Inc.) Lenses are CE-marked and will be used as per their CE marking.
	Route of Administration:	The lenses will be dispensed by a trained unmasked study staff member so that neither the subject nor the Investigator will be able to see the lens label and hence, will remain masked to the identity of the lens. The trained unmasked study staff member will not conduct any of the safety and effectiveness assessments after randomization, [redacted] Subjects will use the lenses as instructed by the investigational site, according to the instructions for use.

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number: CLL541-P001**
	Duration of Lens Wear:	Subjects will wear the lenses bilaterally for a total duration of 30 (+3) days under a daily wear modality for the specific study period. The lenses will be removed every night and cared for with the subject's habitual lens care solution.
	Dosage:	Lenses will be available in the following parameters: Material: senofilcon C, 41% water content Base curve: 8.4, 8.8 mm Diameter: 14.0 mm Rx Range: –0.50 D to -6.00 D (0.25 D steps), -6.50 D to -12.00 D (0.50 D steps), +0.50 D to +6.00 D (0.25 D steps) and +6.50 D to +8.00 D (0.50 D steps)
	Screening Product	[redacted] Lenses are CE-marked and will be used as per their CE marking.
	Route of Administration:	Subjects will use the lenses as instructed by the Study Coordinator or Investigator, according to the instructions for use.
	Duration of Lens Wear:	Subjects will wear the lenses bilaterally for a total duration of 10 hours (± 30 minutes), after which the lenses will be removed to assess lipid uptake of OD lenses.

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	Dosage:	Lenses will be available in the following parameters: Material: balafilcon A, 36% water content Base curve: 8.6 mm Diameter: 14.0 mm Rx Range: 8.6 mm base curve: +6.00 D to -12.00 D (0.25 steps, 0.50 D steps above -6.00 D)
Subject Selection:	**Inclusion Criteria:**	

1. Subjects must be at least 18 years of age and sign the Informed Consent Form

2. Best Corrected Visual Acuity (BCVA) of at least 0.1 logMAR in each eye at Visit 1

3. Manifest cylinder (at Visit 1) less than or equal to 0.75 D in each eye

4. Successful current wearer (during the past 2 months for a minimum of 5 days per week and 8 hours per day) of monthly replacement silicone hydrogel lenses within the power range of lens powers available for the screening and study lenses

5. Screening [redacted] lenses worn 10 hours (± 30 minutes) exhibiting high lipid uptake (see Manual of Procedures)

[redacted]

7. Willing to discontinue artificial tears during the study and rewetting drops on the days of study visits

Exclusion Criteria:

1. Habitual lens used in an extended wear modality (routinely sleeping in lenses overnight for 1 night per week or more) during the past 2 months

2. Habitually wearing AIR OPTIX AQUA, AIR OPTIX plus HydraGlyde, ACUVUE OASYS®, or ACUVUE VITA as contact lenses during the past 2 months

3. Any anterior segment infection, inflammation, disease or abnormality that contraindicates contact lens wear (within 7 days

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of enrolment, or current)

4. History of herpetic keratitis, corneal surgery, or irregular cornea

5. Any use of systemic or ocular medications for which contact lens wear could be contraindicated as determined by the Investigator

6. Any abnormal (Grade 3 or greater) ocular condition observed during the Biomicroscopy examination at Visit 1, Visit 2, or Visit 3 (prior to randomization)

7. Monocular subjects (only one eye with functional vision) or subjects fit with only one lens

8. Known pregnancy and lactation

9. Enrolment of investigational site staff or family/household members of the investigational site staff who are listed on the study personnel log as having a role in the execution of this study

10. Participation in any clinical study within 30 days of Visit 1

Assessments:

Effectiveness:

1. *Ex vivo* lipid uptake of total lipids and individual lipid classes (surface and bulk)

Safety:

1. Biomicroscopy Findings
2. AEs
3. Device Deficiencies

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Statistical Methods:

Planned Analysis

Three analysis sets will be defined. The Safety Analysis Set will include all subjects/eyes exposed to any study lenses (AOHG or VITA). The Full Analysis Set (FAS) will consist of all randomized subjects who are exposed to study lenses (AOHG or VITA).The Per Protocol (PP) Analysis Set will be a subset of all randomized subjects and exclude data/subjects which meet any of the critical deviation or non-evaluable criteria as specified in the Deviations and Evaluability Plan (DEP). The FAS will serve as the primary analysis dataset for all effectiveness evaluations.

All data from evaluable subjects will be included in the respective effectiveness analysis, and no imputation for missing values will be performed.

Effectiveness

The planned analysis to address the primary effectiveness objective is summarized below:

Primary Endpoint	Comparison	Statistical Method
Total lipid uptake (total of surface and bulk uptake) (Day 30)	Superiority	Mixed-effect repeated-measures with terms for lens, period, sequence, and subject. Superiority concluded if 1-sided p-value < 0.05

[redacted]

[redacted]

[redacted]

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[redacted]

Safety

Each safety variable will be summarized descriptively. AEs will be classified as pre-treatment, treatment-emergent, or between-period. Counts and percentages will be provided by relationship to lens, 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. No inferential testing will be performed for the safety analysis.

Sample Size Calculation

Sample size calculation for the primary effectiveness endpoint (1-sided, α=0.05) is summarized below:

Primary Endpoint	Assumptions	Power	N/sequence group
Total lipid uptake (total of surface and bulk uptake)	SD paired differences = 13.88 Detectable difference = 10	80%	7

[redacted]

1.1 Amendments

Amendment 2

Purpose of Amendment: The purpose of this amendment is to address the following items:

Change 1: To expand the time period between Visit 2 and Visit3.

Rationale: The rationale for this change is to allow the laboratory enough time to conduct the evaluation of screening lenses for lipid uptake.

Case Report Form Revision Required:	☐	Yes	☒	No
Informed Consent Modifications Required:	☒	Yes	☐	No
Applicable Investigators:	☒	All	☐	Selected (list below)

Itemized Changes:

Protocol Section	**Information Changed**
Section 2 (Page 14) Overview of Study Plan	*Changed from:* **Visit 3 (Period 1)/ Visit 5 (Period 2)** **Day 1-Insertion** 1 to 14 days from Visit 2 and Visit 4 respectively *No lenses worn* *Changed to:* **Visit 3 (Period 1)/ Visit 5 (Period 2)** **Day 1-Insertion** Within 80 days from Visit 2 and 1 to 14 days from Visit 4, respectively *No lenses worn*

Section 10.2.2 (Page 24) Visits and Examinations: Visit 2 (Screening 2)	Table items #8 *Changed from:* Schedule Visit 3 for eligible subjects to take place 1 to 14 days after Visit 2. Instruct subjects on study compliance requirements. Subjects can wear spectacles or their habitual lenses between Visit 2 and Visit 3. Inform subjects not to wear lenses on the day of Visit 3 and to not use rewetting drops on the day of the visit. Artificial tears must not be used during the study. *Changed to:* Schedule Visit 3 for eligible subjects to take place within 80 days after Visit 2. Instruct subjects on study compliance requirements. Subjects can wear spectacles or their habitual lenses between Visit 2 and Visit 3. Inform subjects not to wear lenses on the day of Visit 3 and to not use rewetting drops on the day of the visit. Artificial tears must not be used during the study.

Change 2: To update the name of the screening lenses.

Rationale: The rationale for this name change is to describe more specifically the screening product name for alignment with other study documents.

Case Report Form Revision Required:	☐	Yes	☒	No
Informed Consent Modifications Required:	☐	Yes	☒	No
Applicable Investigators:	☒	All	☐	Selected (list below)

Itemized Changes:

	[redacted]
Protocol Section	This change was implemented throughout the entire document

Amendment 1

Purpose of Amendment: The purpose of this amendment is to:

1) Clarify the Primary Objective in Section 1 of the protocol.

2) Clarify and elaborate further the background and rationale of this study in Section 5 of the protocol.

3) Update the References in Section 14 of the protocol to correspond to the updated background and study rationale in Section 5.

Rationale: The rationale for this amendment is to elaborate on the study background and rationale, clarify the aim and primary study objective, and update study references.

Current Study Status: Planned; No subjects enrolled at this time

Case Report Form Revision Required:	☐	Yes	☒	No
Informed Consent Modifications Required:	☐	Yes	☒	No
Applicable Investigators:	☒	All	☐	Selected (list below)

Itemized Changes:

Protocol Section	**Information Changed**
Section 1 (Page 2) Synopsis Primary Objective	*Changed from:* The primary objective is to demonstrate superiority of AOHG compared with ACUVUE® VITA® (VITA) in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors. *Changed to:* The primary aim of the study is to confirm that a silicone hydrogel contact lens that attracts lower levels of total lipids *in vitro* (AOHG) also attracts lower levels of total lipids *in*

	vivo compared with a silicone hydrogel contact lens with high *in vitro* lipid attraction (ACUVUE® VITA® (VITA)) in habitual high lipid depositor lens wearers. Therefore, the primary objective is to demonstrate superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.
Section 5.1 (Page 24) Study Rationale and Background	Revised entire section to elaborate on the background and rationale of the study.
Section 14 (Page 59) References	Updated all references to coincide with fully revised study rationale and background in Section 5.1.

2 OVERVIEW OF STUDY PLAN

Assessment	Visit 1 **Screening 1/ Baseline** *Habitual lenses worn*	Visit 2 **Screening 2** 1 to 7 days from Visit 1 After 10 h (± 30 min) wear of [redacted]	Visit 3 (Period 1)/ Visit 5 (Period 2) **Day 1-Insertion** Within 80 days from Visit 2 and 1 to 14 days from Visit 4 respectively *No lenses worn*	Visit 4 (Period 1)/ Visit 6 (Period 2)/ Study Exit **Day 30 (+3 days)** After 10 h (± 30 min) wear of study lenses **Early Exit**	USV
Informed Consent	V				
Randomization			V[a]		
Demographics	V				
Medical History/CL wear history	V				
Concomitant Medications	V	V	V	V	V
Inclusion/Exclusion	V	V	V		
[redacted]					
Conduct a spherical over-refraction and optimize the Rx as required	V[b]		V		
LogMAR VA with lenses	V[b]		V	V	(V)
BCVA with Manifest Refraction[c]	V	V	V	V	V
Biomicroscopy	V	V	V	V	V
[redacted]					
Assess Lens Fit	V[c, e]		V	V	
[redacted]					

Assessment	Visit 1 **Screening 1/ Baseline** *Habitual lenses worn*	Visit 2 **Screening 2** 1 to 7 days from Visit 1 After 10 h (± 30 min) wear of [redacted]	Visit 3 (Period 1)/ Visit 5 (Period 2) **Day 1-Insertion** Within 80 days from Visit 2 and 1 to 14 days from Visit 4 respectively *No lenses worn*	Visit 4 (Period 1)/ Visit 6 (Period 2)/ Study Exit **Day 30 (+3 days)** After 10 h (± 30 min) wear of study lenses **Early Exit**	USV
Provide [redacted] lenses for 10 h (± 30 min) of wear on the day of Visit 2	V				
Collect 10-h worn [redacted] lenses for *ex vivo* total lipid uptake analysis		V[f]			
Collect study lenses for all *ex vivo* lipid uptake analyses				V	
Complete Exit Form	(V)	(V)	(V)	V	(V)
Assess AEs (observed and reported)	V[g]	V	V	V	V
Assess Device Deficiencies	V	V	V	V	V

a) Randomization to be performed after the Biomicroscopy examination

b) Visit 1 with habitual lenses [redacted]

c) Source document only

[redacted]

e) With [redacted] lenses

f) Confirm scheduling of Visit 3 after [redacted] *ex vivo* lipid analysis is complete and eligibility confirmed

g) AEs will be collected from the time of Informed Consent.

(V) As needed or if a 2-line change in Contact Lens Corrected logMAR VA is observed

AE = adverse event, BCVA = Best Corrected Visual Acuity, CL = contact lens, [redacted], h = hours, logMAR = logarithmic Minimum Angle of Resolution, min = minutes, [redacted], USV = unscheduled visit, VA = visual acuity

3 ABBREVIATIONS AND GLOSSARY OF TERMS

3.1 List of abbreviations

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
AOHG	AIR OPTIX plus HydraGlyde
BCVA	Best corrected visual acuity
CE	*Conformité Européenne*
CL	Contact lens
[redacted]	[redacted]
D	Diopter
DEP	Deviations and evaluability plan
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
[redacted]	[redacted]
GCP	Good Clinical Practice
h	Hours
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IEC	Independent ethics committee
ISO	International Organization for Standardization
logMAR	Logarithmic minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
min	Minutes
mm	Millimeter
[redacted]	[redacted]
NI	Noninferiority
OD	Right eye
OS	Left eye
OU	Both eyes
PP	Per protocol
Rx	Prescription
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
[redacted]	[redacted]
USV	Unscheduled visit
VA	Visual acuity
[redacted]	[redacted]

Abbreviation	Definition
VITA	ACUVUE VITA

3.2 Glossary of Terms

Adverse Event	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	Adverse event related to the use of an investigational medical device (test article) or control article. *Note: This definition includes AEs 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 AE 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	Adverse event that led to any of the following: - Death - A serious deterioration in the health of the subject that either resulted in: 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, ie, 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 c) In-patient hospitalization or prolonged hospitalization *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered an SAE. 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 AEs. 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.* 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, or a congenital abnormality or birth defect. *Refer to Section 12 for additional SAEs.*
Serious Adverse Device Effect	Adverse device effect that has resulted in any of the consequences characteristic of an SAE.
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 or Creutzfeldt-Jacob Disease.
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.*

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5 INTRODUCTION

5.1 Study Rationale and Background

Dryness is the most common complaint of contact lens wearers and is the primary reason for contact lens wear discontinuation (Young 2011). Silicone hydrogel contact lenses have become the standard of care for contact lens correction, as that class of material provides oxygen transmissibility to a level that fulfills the oxygen requirement for uncompromised anterior eye physiology. Despite their desirable physiological and mechanical properties, silicone hydrogel contact lenses have been associated with increased spoliation by tear film lipids (Maissa 2014, Jones 2003), and in some cases reduced wettability (Keir 2013), because of the inclusion of hydrophobic siloxane components into the materials.

In order to counter the hydrophobic effect of silicone material on *in vivo* contact lens wettability, surface-based approaches such as plasma surface technology or incorporation of wetting agents have been used to enhance the wettability and ocular biocompatibility of silicone hydrogel contact lenses. It has been shown that these approaches are differentially effective at reducing lipid deposition both *in vitro* (Pucker 2010) and *ex vivo* (Nash 2014, Zhao 2009); and for a given lens material, there is a large variation in lipid uptake amongst the population (Maissa 2014).

It is desirable to understand how lipid deposition affects the clinical performance of the lenses over the replacement period; however, some key questions of clinical importance remain unanswered. For example:

Where does lipid deposition occur?

- At the surface, in the bulk, or both?

[redacted]

Answers to these questions could lead to scientifically based advice in choosing contact lenses for heavy depositors, and to date no information is available.

In order to understand the effect of lipid deposition on [redacted] silicone hydrogel lenses over a full month of wear, 2 monthly replacement silicone hydrogel lenses with different wettability improvement approaches will be studied: lotrafilcon B lenses with plasma surface treatment (Alcon Air Optix plus HydraGlyde; AOHG) and senofilcon C

lenses with added internal wetting agent (Johnson &Johnson Acuvue Vita; VITA). It has been shown that these 2 lens materials deposit lipids to a different degree; the test lotrafilcon B lenses tend to resist lipid deposition while the control senofilcon lenses tend to uptake lipids to a greater degree (Nash 2014, Zhao 2009). Additionally, a population of known lipid depositors will be targeted for enrollment in order to appropriately assess the patient population of interest. [redacted]

In summary, the aim of the present study is to compare the [redacted] laboratory performance of AOHG and VITA in high lipid depositors to understand the lipid deposition location and profile of each lens after 30 days of wear [redacted]

5.2 Known and Potential Risks

The participants in this study will be current daily wearers of 1-month replacement CE-marked silicone hydrogel contact lenses. Participation in the study will not result in a change of treatment as they will continue to wear different types of 1-month replacement CE-marked silicone hydrogel contact lenses under the same conditions and using their habitual lens care system. Hence, participation in the study does not increase the potential risks associated with daily contact lens wear. Safety information details on the study contact lenses are found on the manufacturer's users' leaflets, which will be supplied to the participants. In addition, the Investigator will advise participants of the general warnings and precautions associated with contact lens wear:

- Serious eye injury, scarring of the cornea and loss of vision may result from problems associated with wearing contact lenses and using lens care products
- Eye problems, including infection, corneal ulcers, corneal neovascularization or iritis can develop rapidly and lead to loss of vision if left unattended
- Smoking and/or swimming increase the risk of corneal ulcers with contact lens wear, especially when lenses are worn overnight or while sleeping
- The risk of ulcerative keratitis has been shown to be greater among users who wear their lenses overnight compared with those who do not

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.

Subjects will be instructed to use study lenses as daily wear according to the Instructions for Use and/or following the instructions from the Investigator. Subjects who fail to follow the instructions for replacing their contact lenses could experience an eye infection of the cornea or an eye injury. A corneal ulcer could develop rapidly and lead to loss of vision. An improperly fitted contact lens may affect corneal curvature and result in vision fluctuations upon lens removal.

Potential serious complications with contact lens wear are usually accompanied by one or more of the following signs or symptoms:

Moderate to severe eye pain not relieved by removing the lens

Foreign body sensation

Excessive tearing/ocular secretions including mucopurulent discharge

Ocular hyperemia

Photophobia

Burning, stinging, itching, or other pain associated with the eyes

Less comfort than when the lens was first placed on the eye

Poor visual acuity/blurred vision

Rainbows or halos around objects

Feeling of dryness

Subjects should be instructed to remove the lenses if any of the above signs or symptoms is noticed. A serious condition such as corneal ulcer, infection, or iritis may be present, and may progress rapidly. Less serious reactions such as abrasions, infiltrates, and bacterial conjunctivitis must be managed to avoid more serious complications.

In addition, the Investigator should advise subjects of possible ocular dryness, increased lens awareness/intolerance, visual changes with concomitant medications or during pregnancy. The Investigator must assess for ocular changes to determine whether to discontinue or restrict lens wear, eg, ocular infections, tarsal papillary changes, local or generalized corneal edema, epithelial microcysts, epithelial staining, infiltrates, neovascularization, endothelial polymegathism, conjunctival injection, and iritis.

5.3 Potential Benefits

Material properties and design characteristics of contact lenses used in this study are features consistent with successful contact lens wear. This study provides participants with the opportunity to try new contact lenses which they may find preferable to their habitual lenses.

6 ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the ICH E6 GCP Consolidated Guideline, ISO 14155: 2011 Clinical investigation of medical devices for human subjects, and other regulations as applicable. The Investigator and all 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, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an Independent Ethics Committee (IEC). The Investigator must provide documentation of the IEC approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), Informed Consent Form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IEC must be provided any periodic safety updates, and all other information as required by local regulation and/or the IEC. At the end of the study, the Investigator will notify the IEC about the study's completion. The IEC will also be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC on the progress of the study at intervals stipulated by the IEC.

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 Informed Consent Form 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 AOHG, VITA, [redacted] 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 prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

This is the second amended version of this protocol.

8 SUBJECT POPULATION

The study population includes approximately 140 volunteer subjects to be screened (enrolled) at 1 investigational site in the United Kingdom. Of the 140 screened subjects, approximately 78 will be randomized to achieve 70 subjects to complete the study.

To participate in the study, subjects must be at least 18 years of age, with healthy eyes, be classified a high lipid depositor, and be successful current wearers of monthly replacement silicone hydrogel lenses within the power range of lens powers available for the screening and study lenses. The expected duration of subject participation in the study is approximately 3 months. The complete inclusion and exclusion criteria are presented in Section 1.

Any advertisements that may be used to aid recruitment will be submitted to the IEC for approval prior to use.

9 TREATMENTS ADMINISTERED

Upon signing the Informed Consent Form at Visit 1, subjects will be considered enrolled in the study and a subject identification (ID) number will be assigned by entering the subject into the electronic data capture (EDC) system by a designated staff member at the investigational site. At Visit 3, eligible subjects will be randomized in a 1:1 ratio to wear AOHG in Period 1 and VITA in Period 2, or the other way around (VITA in Period 1 and AOHG in Period 2). Throughout the study, the Investigator should ensure the unmasked study staff member is responsible for the accounting of all screening and study lenses and guarantees that they are not used in any unauthorized manner.

9.1 Identity of Study Treatments

The spherical contact lenses to be used in the study will be:

Screening Product: [redacted]

Investigational Product: AIR OPTIX plus HydraGlyde

Control Product: ACUVUE VITA

The AOHG and VITA lenses will be dispensed in a masked manner (removal of blister labels) by a trained unmasked study staff member so that neither the subject nor the Investigator can see the lens label and remain masked to the details of the lenses. All screening and study lenses are CE-marked and will be procured by the investigational site. No over-labelling is required. Storage conditions for the screening and study lenses are documented in their respective packaging and labelling.

9.2 Usage

The subjects will use the screening and study lenses according to the Instructions for Use provided by the product manufacturer, in addition to following the instructions from the designated investigational site staff. AOHG and VITA lenses will be prepared by a trained unmasked study staff member and dispensed to subjects.

Subjects will wear the screening [redacted] lenses for 10 hours (± 30 minutes) on the day of Screening 2, Visit 2. Subjects will wear the AOHG and VITA lenses for a total duration of 30 days (+3 days) each under a daily wear modality for the assigned study period. The lenses will be removed every night and cared for with the subject's habitual lens care solution.

Subjects will be instructed not to use artificial tears throughout the study and not to use rewetting drops on the day of their study visits. Subjects should attend Visit 1 wearing their habitual lenses. Visit 2 should occur after 10 hours (± 30 minutes) of wear of [redacted] lenses. Visit 4 and Visit 6 should occur after 10 hours (± 30) minutes of study lens wear. No lenses should be worn on the days of Visit 3 and Visit 5 until study lenses are dispensed at the study visit.

Between Screening Visits 1 and 2, between Screening Visit 2 and Period 1-Day 1, and between Period 1-Day 30 and Period 2-Day 1, subjects may wear spectacles or return to habitual lens wear; however as a washout, no lenses are to be worn prior to the visits on the insertion days (Period 1-Day 1 and Period 2-Day 1).

9.3 Accountability Procedures

Upon receipt of the study and screening lenses, the Investigator or designee will conduct an inventory. Unmasked study staff will prepare the study lenses for the subjects (by removing blister labels) in accordance with the randomized order assigned in EDC. The identity of the study lenses will not be revealed to the subject or the Investigator.

During the study, the unmasked study staff member must maintain records of screening and study lens dispensation and collection for each subject. 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.

Alcon lenses associated with a Device Deficiency or with any product-related AEs must be returned to the Sponsor. Refer to Section 12 of this protocol for additional information on the reporting of Device Deficiency or product-related AEs, and to the Manual of Procedures for return address and instructions.

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 number and date of birth of each study participant. At the end of the study, the Sponsor will collect a copy of the enrollment log without any information identifying the subjects. All documents submitted to the Sponsor will identify the subjects exclusively by number 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 study. Bias could arise from the influence that the knowledge of a specific lens assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of endpoints, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the Investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

This study is double-masked, with subjects randomized to receive 1 of 2 possible sequences of study lenses: AOHG then VITA, or VITA then AOHG. The Investigator, the subject, and the investigational site staff involved in reporting, obtaining, and/or reviewing the clinical evaluations will not be aware of the specific lens being worn. To achieve this, the study lenses will be fit and dispensed by a designated unmasked member of study staff not involved in the collection or measurement of any safety or effectiveness endpoints. From the Sponsor, Alcon study personnel will be masked, with the exception of a designated data manager, the lead monitor, the site monitor, and the person responsible for generating the randomization schedule.

This level of masking will be maintained throughout the conduct of the study. Subjects will be assigned a lens sequence in numerical order. The randomization scheme will be generated and maintained by the Sponsor. Only when all study data have been verified and validated, and the database locked, will individual subjects be unmasked. 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 lens assignment for a specific subject.

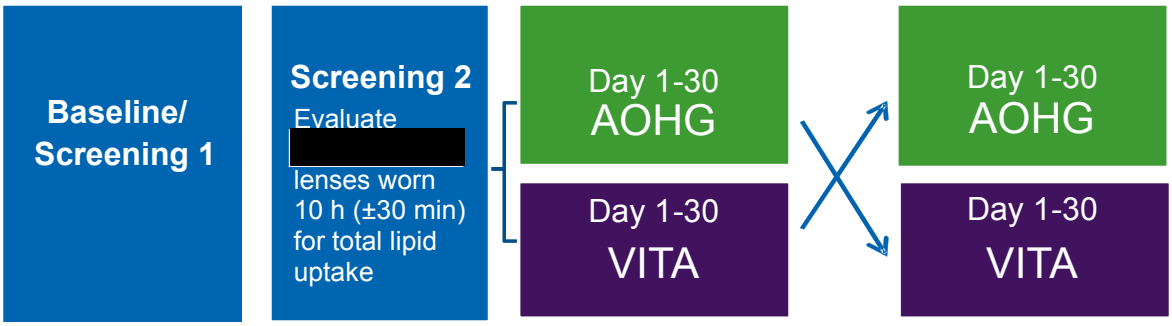
10 STUDY PROCEDURES

10.1 Outline of the Study

This is a prospective, randomized (lens sequence), double-masked, crossover study (Figure 10-1). The study population will include approximately 78 randomized subjects who are high lipid depositors with normal eyes (other than correction for refractive error), at least 18 years of age, and are successful current wearers of monthly replacement silicone hydrogel contact lenses.

At Visit 1, subjects will be assessed for their suitability based upon their habitual lens wear and if eligible, they will be dispensed [redacted] lenses. Subjects should wear their [redacted] lenses for 10 hours (± 30 minutes) on the day of Visit 2, at which the lenses will be removed and the total lipid uptake of those worn on the right eyes will be analyzed. If the total lipid uptake classifies the subject as a high lipid depositor, and all other inclusion/exclusion criteria are still met, the subject will continue and be randomized at Visit 3. The subject will attend 3 additional visits and will wear the study lenses for 2 periods of 30 (+3) days each.

Figure 10–1 Study Diagram



10.2 Visits and Examinations

Full details of the assessments for this study are described in the CLL541-P001 Manual of Procedures.

10.2.1 Visit 1 (Screening 1/Baseline)

1.	Explain the purpose and nature of the study, and have the subject or legally authorized representative read, sign, and date the IEC-approved Informed Consent Form. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the Informed Consent Form. Provide a photocopy of the signed document to the subject and place the original signed Informed Consent Form in the subject's chart.
2.	Record and assess any AEs and Device Deficiencies that are reported or observed from the time of Informed Consent
3.	Assign the subject a 5-digit Subject Number obtained from the EDC *Note: Assign subject numbers for all subjects who sign the Informed Consent Form (including screen failures)*
4.	Obtain demographic information, habitual lens information, and medical history 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.
[redacted]	
6.	Conduct a spherical over-refraction and optimize the Rx as required
7.	Assess monocular logMAR VA with habitual lenses (with and without spherical over-refraction) (only record habitual contact lens corrected VA without spherical over-refraction in EDC)
[redacted]	
9.	Have the subjects remove habitual lenses
10.	Assess biomicroscopy
11.	Determine Manifest Refraction (sphero-cylindrical and best sphere) and measure monocular logMAR BCVA
12.	Assess inclusion/exclusion criteria *Note: Inclusion #5 (Screening [redacted] lenses worn 10 hours [± 30 minutes] exhibiting high lipid uptake) will be assessed after the lenses are collected at Visit 2*
13.	Insert [redacted] screening lenses (at least 10 minutes wearing time)

14.	Verify contact lens fit and change [redacted] screening lenses with different base curve if fit is not satisfactory Conduct a spherical over-refraction and optimize the Rx as required
15.	Assess monocular logMAR VA with [redacted] lenses (with and without spherical over-refraction) (record in source)
[redacted]	
17.	Remove [redacted] trial screening lenses
18.	If subject is suitable for participation, provide a new pair of [redacted] lenses (including information for use) to be worn before Visit 2 for 10 hours (± 30 minutes) of wear on the day of Visit 2
19.	Schedule Visit 2 to take place 1 to 7 days after Visit 1. Instruct subjects on study compliance requirements. Subjects may wear spectacles or their habitual lenses until Visit 2. Remind the subject that on the day of Visit 2 to have worn the [redacted] lenses for at least 10 hours (± 30 minutes) and to not use rewetting drops on the day of the visit. Artificial tears must not be used during the study

10.2.2 Visit 2 (Screening 2)

1.	Obtain information on any changes in medical health, and/or the use of concomitant medications
2.	Record any AEs, including those associated with changes in concomitant medication dosing and Device Deficiencies that are observed or reported
3.	Review subject compliance with lens wear (10 hours [± 30 minutes] of wear on day of visit) and confirm no use of artificial tears during the study as well as no use of rewetting drops on the day of study visit
4.	Perform aseptic contact lens removal and storage in freezer of 10-hour worn [redacted] lenses for *ex vivo* total lipid uptake analysis
5.	Assess biomicroscopy
6.	Assess monocular logMAR BCVA
7.	Confirm subject eligibility *Note: Confirm scheduling of Visit 3 after* [redacted] *ex vivo lipid analysis is complete and eligibility confirmed*
8.	Schedule Visit 3 for eligible subjects to take place within 80 days after Visit 2. Instruct subjects on study compliance requirements. Subjects can wear spectacles or their habitual lenses between Visit 2 and Visit 3. Inform subjects not to wear lenses on the day of Visit 3 and to not use rewetting drops on the day of the visit. Artificial tears must not be used during the study.

10.2.3 Visit 3 (Day 1-Insertion Period 1)

1.	Obtain information on any changes in medical health and/or the use of concomitant medications
2.	Record any AEs, including those associated with changes in concomitant medication dosing and Device Deficiencies that are observed or reported
3.	Confirm subject compliance with no lens wear and confirm no use of artificial tears during the study as well as no use of rewetting drops on the day of study visit
4.	Assess monocular logMAR BCVA
5.	Assess biomicroscopy
6.	Confirm subject eligibility and randomize eligible subjects by entering details of eligibility into EDC system and obtain assignment of lens sequence
7.	Administer randomized study lenses no earlier than 15 minutes after biomicroscopy, record time of insertion
[redacted]	
9.	Verify Lens Fit approximately 15 minutes after insertion *Note: if the fit of the control contact lens is not suitable the contact lens needs to be removed and the alternative base curve tried*
10.	Conduct a spherical over-refraction and optimize the Rx as required (binocular optimization)
11.	Assess monocular logMAR VA with lenses (with and without spherical over-refraction) (record VA with study lenses and without spherical over-refraction in EDC)
[redacted]	
17.	Schedule Visit 4 to take place on Day 30 (+ 3). Instruct subjects on study compliance requirements and remind the subject to wear the lenses for 10 hours ± 30 minutes on the visit day, and not to use artificial tears during the study period nor rewetting drops on the day of the visit. Instruct subjects to use habitual lens care to care for their lenses daily.

10.2.4 Visit 4 (Day 30 Period 1)

1.	Obtain information on any changes in medical health and/or the use of concomitant medications
2.	Record any AEs, including those associated with changes in concomitant medication dosing and Device Deficiencies that are observed or reported
3.	Confirm subject compliance with lens wear and confirm no use of artificial tears during the study as well as no use of rewetting drops on the day of study visit
4.	Assess subjective acceptance of study lenses
5.	Assess monocular logMAR VA with lenses (with and without spherical over-refraction) (record VA with study lenses and without spherical over-refraction in EDC)
[redacted]	
9.	Assess Lens Fit
10.	Aseptic contact lens removal and storage in freezer of study lenses for *ex vivo* lipid uptake analysis ((total, individual, surface, bulk))
11.	Assess biomicroscopy
12.	Assess monocular BCVA with Manifest Refraction
13.	Schedule Visit 5 to take place 1 to 14 days after Visit 4. Instruct subjects on study compliance requirements. Subjects can wear spectacles or their habitual lenses between Visit 4 and Visit 5. Inform subject not to wear lenses on the day of Visit 5, to not use artificial tears during the study, and not to use rewetting drops on the day of the visit

10.2.5 Visit 5 (Day 1-Insertion Period 2)

1.	Obtain information on any changes in medical health and/or the use of concomitant medications
2.	Record any AEs, including those associated with changes in concomitant medication dosing and Device Deficiencies that are observed or reported
3.	Confirm subject compliance with no lens wear and confirm no use of artificial tears during the study as well as no use of rewetting drops on the day of study visit
4.	Assess monocular logMAR BCVA
5.	Assess biomicroscopy
6.	Administer randomized study lenses no earlier than 15 minutes after biomicroscopy, record time of insertion
[redacted]	
8.	Verify Lens Fit approximately 15 minutes after insertion *Note: if the fit of the control contact lens is not suitable the contact lens needs to be removed and the alternative base curve tried*
9.	Conduct a spherical over-refraction and optimize the Rx as required (binocular optimization)
10.	Assess monocular logMAR VA with lenses (with and without spherical over-refraction) (record VA with study lenses and without spherical over-refraction in EDC)
[redacted]	
15.	Schedule Visit 6 to take place at Day 30 (+3). Instruct subjects on study compliance requirements. Inform subject to wear the lenses for 10 hours ± 30 minutes on the visit day and not to use artificial tears during the study period or rewetting drops on day of visit. Instruct to use habitual lens care to care for their lenses daily

10.2.6 Visit 6 (Day 30 Period 2 - Last Study Visit – Exit)

1.	Obtain information on any changes in medical health and/or the use of concomitant medications
2.	Record any AEs, including those associated with changes in concomitant medication dosing and device deficiencies that are observed or reported
3.	Confirm subject compliance with lens wear and confirm no use of artificial tears during the study as well as no use of rewetting drops on the day of study visit
4.	Assess subjective acceptance of study lenses
5.	Assess monocular logMAR VA with lenses (with and without spherical over-refraction) (record VA with study lenses and without spherical over-refraction in EDC)
[redacted]	
9.	Assess Lens Fit
10.	Aseptic contact lens removal and storage in freezer of study lenses for *ex vivo* lipid uptake analysis ((total, individual, surface, bulk))
11.	Assess biomicroscopy
12.	Assess monocular BCVA with Manifest Refraction
13.	Exit 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 electronic Case Report Form (eCRF).

If a subject needs a lens replacement, an unscheduled visit should be performed. Subjects will not restart the study period in the case of an unscheduled lens replacement.

During all unscheduled visits, the following procedures should be conducted:

1.	Obtain information on any changes in medical health and/or the use of concomitant medications
2.	Record any AEs, including those associated with changes in concomitant medication dosing and Device Deficiencies that are observed or reported
3.	Assess monocular logMAR VA with lenses (as needed)
4.	Assess monocular BCVA with Manifest Refraction
5.	Assess biomicroscopy

If the subject discontinues at the unscheduled visit, all the assessments listed for Visit 4/Visit 6 should be performed. The Exit Form should also be completed.

10.4 Screen Failures

Subjects who do not meet inclusion/exclusion criteria for study participation will be considered screen failures and must not be re-screened.

10.5 Discontinued Subjects

Discontinued subjects will include those who withdraw or are withdrawn from the study after randomization at Visit 3. 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).

Should a subject exhibit any clinically relevant signs, symptoms, or other clinical observations that could possibly be associated with suspected sensitivity or intolerance to one of the study lenses, the Investigator must document those observations on an AE Form.

Any subject who exits early from the study should undergo all procedures outlined at Visit 4/Visit 6. Additionally, the Exit Form must be completed and the reason for discontinuation identified.

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

10.6 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 reasons thereof. The Investigator should promptly notify the IEC of the termination/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 any 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 effectiveness

Inadequate recruitment of subjects by the Investigator

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

11 ANALYSIS PLAN

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum and maximum, as well as confidence intervals or confidence limits 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 sequence assignment and locking the database, based upon the DEP.

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 any study lenses (AOHG or VITA) evaluated in this study. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual lens exposed.

11.2.2 Full Analysis Set

The FAS is the set of all randomized subjects who are exposed to any study lenses (AOHG or VITA) evaluated in this study.

11.2.3. Per Protocol Analysis Set

The PP Analysis Set is a subset of all randomized subjects and excludes all data/subjects that meet any of the critical deviation or non-evaluable criteria identified in the DEP.

11.3 Demographic and Baseline Characteristics

Demographic information (age and sex) will be summarized for the Safety, Full, and PP Analysis Sets. Baseline characteristics on habitual lenses [redacted] and VA will be summarized for the Full and the PP Analysis Sets.

11.4 Effectiveness Analyses

This study defines 1 primary, [redacted] endpoints. All effectiveness evaluations will use the FAS as the primary analysis set.

Supportive analyses of the primary [redacted] endpoints will be conducted using the PP Analysis Set only if the number of subjects excluded from the PP analysis set exceeds 5% of the FAS.

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

11.4.1. Primary Effectiveness Analysis

The primary objective of this study is to demonstrate superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.

The corresponding endpoint is the total amount of lipids (µg) absorbed/adsorbed and extracted (total of surface and bulk uptake) from worn test and control lenses at Day 30. Only OD lenses will be used for the *ex vivo* analysis.

11.4.1.1. STATISTICAL HYPOTHESES

The null and alternative hypotheses are formulated as follows:

H_0: $\mu_T - \mu_C \geq 0$

H_a: $\mu_T - \mu_C < 0$

where μ_T and μ_C represent the mean total lipid uptake (total of surface and bulk uptake) measured from the test and control lenses, respectively.

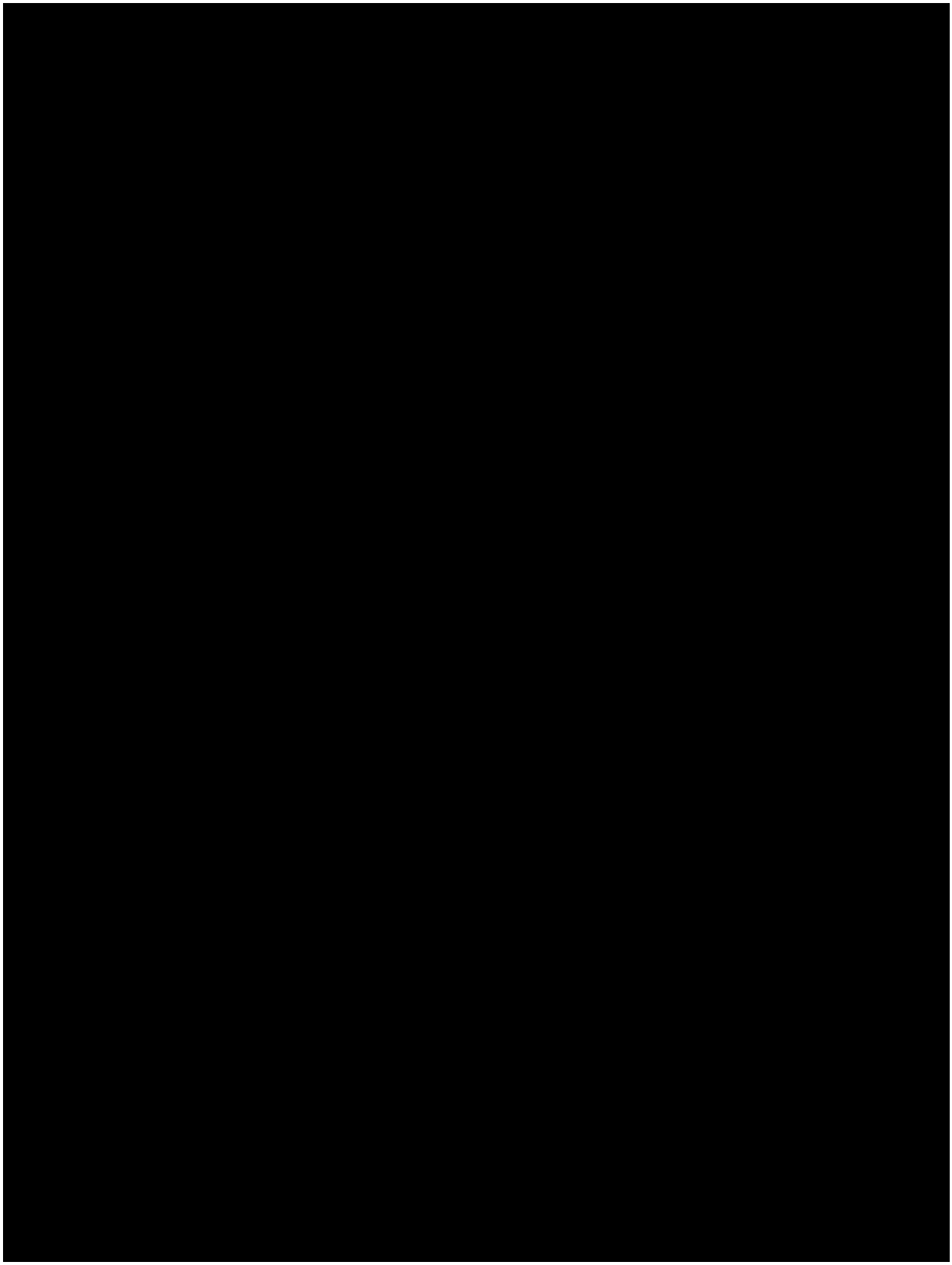
11.4.1.2. ANALYSIS METHODS

A mixed effect repeated measures model will be fit to test these hypotheses. To account for within-subject correlation due to crossover, the model will include terms for lens, period, and lens sequence group as fixed effects and subject as a random effect. Normality will be checked. If the normality assumption does not hold, a natural log transformation will be performed as $\log_e(\mu g+1)$.

11.4.2. Secondary Effectiveness Analysis

No secondary effectiveness objective is defined for this study.

[redacted]



[redacted]

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 effectiveness analysis.

[redacted]

[redacted]

11.7. Safety Analysis

The safety endpoints for this study are Biomicroscopy Findings, AEs, 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, relationship to lens will be identified. Serious Adverse Events will also be tabulated separately. Individual subject listings will be provided, as necessary.

Additionally, individual subject listings will be provided for AEs that:

- Occur after signing the Informed Consent Form, but prior to exposure to test or control lenses (pre-treatment)
- Occur after last exposure to Period 1 lenses, but prior to exposure to Period 2 lenses (between-period)

Each Biomicroscopy parameter will be tabulated by its grade. Counts and percentages of eyes that experience an increase of ≥ 2 grades from Visit 3/Visit 5 to any subsequent visit within each period will be presented. A supportive listing will be generated which will include all Biomicroscopy data from the visits within each affected period for those eyes experiencing the increase of ≥ 2 grades, with the following variables: lens, Investigator, subject, age, sex, visit, eye, parameter, baseline value, and value at the visit.

Frequency counts will be tabulated for each Device Deficiency category. Additionally, 2 listings will be provided: prior to exposure to study lens and treatment-emergent.

No inferential testing will be done for the safety analysis.

11.8. Health Economics

Not applicable.

11.9. Interim Analyses

Not applicable.

11.10 Sample Size Justification

[redacted]

Sample sizes per sequence group required to attain 80% power at 1-sided, α=0.05 for the primary [redacted] endpoints are shown below:

Endpoint	Assumptions	N/sequence group
Primary		
Ex vivo total lipid uptake (total of surface and bulk uptake)	SD paired differences = 13.88 Detectable difference = 10	7 (based upon t-test for difference of means in 2x2 crossover design)

[redacted]

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 study lenses. For categories of AEs and SAEs, refer to the Glossary of Terms (see also Figure 12-1 and Figure 12-2).

Figure 12–1 Categorization of all Adverse Events

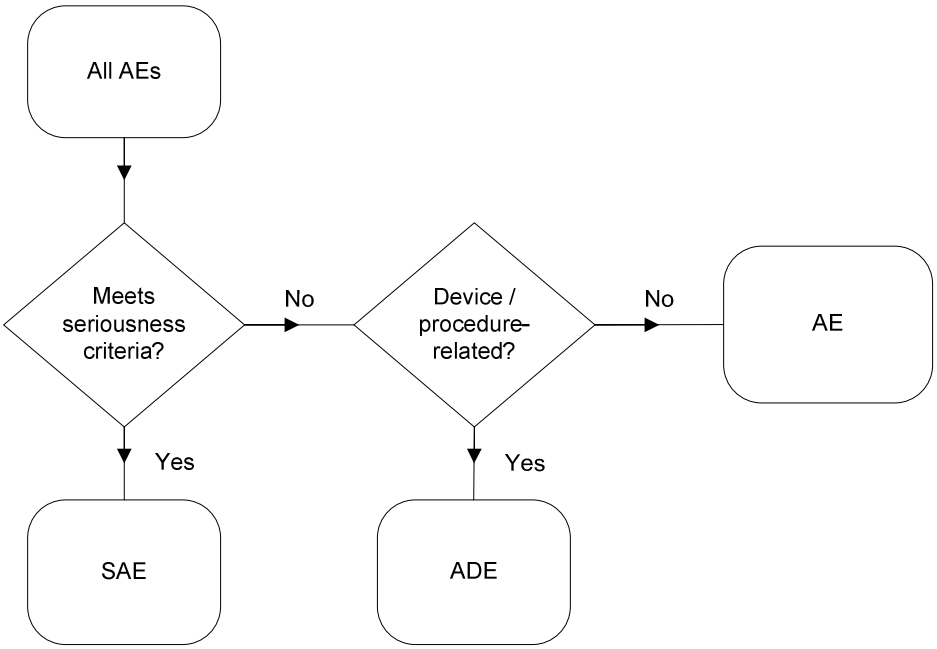
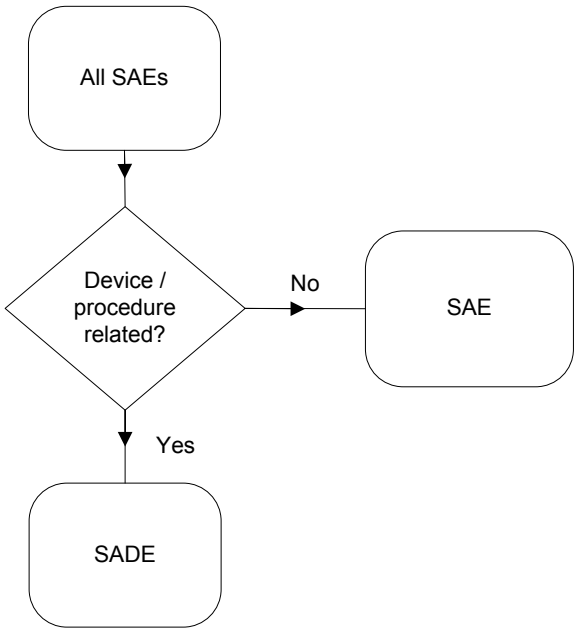


Figure 12-2 Categorization of all Serious Adverse Events



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 (if applicable)* 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 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 will be 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) will not be considered AEs in the study and should be recorded in the Medical History section of the eCRF.

In addition, temporary lens awareness or visual changes during the fitting process will not be considered AEs if the Investigator assesses that the symptom(s) can reasonably resolve within the anticipated adaptation period.

For each recorded event, the Adverse Device Effects (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 test and control articles on the Device Deficiency eCRF. The investigational site must submit all available information on ADEs, SAEs, and Device Deficiencies to the Sponsor immediately as follows:

All SAEs must be reported immediately (within 24 hours) of the Investigator's or investigational site's awareness

Adverse device effects that do not meet the seriousness criteria, and Device Deficiencies must be reported within 10 calendar days of the Investigator's or investigational 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 (refer to CLL541-P001 Manual of Procedures for details on the return instructions)

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 the narrative section of the Adverse Device Effect (for related AEs) and Serious Adverse Event eCRF

Note: Should the EDC system become non-operational, the investigational site must complete the appropriate paper ***Serious Adverse Event and Adverse Device Effect*** **and/or** ***Device Deficiency*** **Form. The completed form is emailed to the Sponsor at ftw.medical_safety@alcon.com** according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

Additionally, any AEs and Device Deficiencies for non-study marketed products (ie, [redacted] contact lenses, [redacted]) will be considered and processed as spontaneous (following the post-market vigilance procedures) and should be communicated to the product's manufacturer as per local requirements.

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

Further, depending upon the nature of the AE or device deficiency being reported, the 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 Serious Adverse Device Effect (SADE) according to the requirements of regulatory authorities or IEC.

Intensity and Causality Assessments

Where appropriate, the Investigator must assess the intensity (severity) of the AE based upon 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 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 Sponsor will assess the AEs and may upgrade the Investigator's assessment of seriousness and/or causality. The Sponsor will notify the Investigator of any AEs that is upgraded from non-serious to serious or from unrelated to related.

12.4 Return Product Analysis

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

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

12.5 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study (see Section 9.4 for details on the masking procedure). If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate 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 Sponsor. The Sponsor must be informed of all cases in which the code was broken and of the circumstances involved. Additionally, the Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

12.6 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 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 the time of subject's exit from the 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 post-market 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.

12.7 Pregnancy in the Clinical 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 investigational 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

Study product 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 study completion and reason for early discontinuation, if applicable

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.

The eCRFs will be provided to the investigational sites; only designated individuals may complete the eCRFs. The eCRFs will be submitted at regular intervals based upon the clinical study 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.

13.2 Data Review and Clarifications

The eCRF data will be reviewed against the subject's source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the investigational 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).

The results of the study are intended for publication to support future product information.

13.4 Quality Assurance and Quality Control

The Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements. The Sponsor will secure agreement from all involved parties to ensure direct access to the study-related investigational site, source data and documents, and reports for the purpose of monitoring and auditing by the 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 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.

14 REFERENCES

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12/07/2017 20:11:04	[redacted]	[redacted]
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