Clinical Study Protocol
Johnson & Johnson Vision Care, Inc.

Protocol Title
Late Night Study 2: End-of-Day Assessment of Asymptomatic and Symptomatic Soft Lens Wearers

Protocol CR-6290 [redacted]

Version: 6.0 Amendment 5

Date: 23 September 2020

Investigational Products: Dailies AquaComfort Plus, Acuvue Oasys 1-Day

Key Words: asymptomatic, symptomatic, comfort, end-of-day, Dailies AquaComfort Plus (nelfilcon A), Acuvue Oasys 1-Day (senofilcon A), daily wear, daily disposable, dispensing, osmolarity, non-invasive break up time, tear meniscus height, lid margin staining, confocal microscopy

Statement of Compliance to protocol, GCP and applicable regulatory guidelines:
This trial will be conducted in compliance with the protocol, ISO 14155,[1] the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP),[2] the Declaration of Helsinki,[3] and all applicable regulatory requirements.

Confidentiality Statement:

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SPONSOR NAME AND ADDRESS

Johnson & Johnson Vision Care (JJVC)
7500 Centurion Parkway
Jacksonville, FL 32256

MEDICAL MONITOR

Name: [redacted]
Title: [redacted]
Address: [redacted]
Email: [redacted]
Fax#: [redacted]

The Medical Monitor must be notified by the clinical institution/site by e-mail, fax, or telephone within 24 hours of learning of a Serious Adverse Event. The Medical Monitor may be contacted during business hours for adverse event questions. General study related questions should be directed towards your assigned clinical research associate.

The Medical Monitoring Plan is maintained as a separate document and included in the Trial Master File.

AUTHORIZED SIGNATURES

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations,[4] ICH guidelines,[2] ISO 14155,[1] and the Declaration of Helsinki.[3]

Author

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Study Responsible Clinician

See Electronic Signature Report

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Clinical Operations Manager

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Medical Safety Officer	See Electronic Signature Report [redacted]	DATE
Reviewer	See Electronic Signature Report [redacted]	DATE
Approver	See Electronic Signature Report [redacted]	DATE

CHANGE HISTORY

Version	Originator	Description of Change(s) and Section Number(s) Affected	Date
1.0	[redacted]	Original Protocol	22 January 2019
2.0	[redacted]	Updated base curve value of the Acuvue OASYS lens, updated slit lamp procedures concerning timing of lid eversion, corrected error in exclusion #13 Added package insert for Dailies AquaComfort Plus	27 February 2019
3.0	[redacted]	Corrected lens fit assessment parameters	06 March 2019
4.0	[redacted]	Removed need to collect worn lenses for analysis Specified subjective grading of lid margin staining from photos Ancillary supplies table updated	16 April 2019

5.0	[redacted]	To enable recruitment of the targeted number of symptomatic subjects, the total number of subjects which can be enrolled was increased. Study responsible clinician at JJVC changed to [redacted]. Clarified numbering of visits in Part 2.	30 October 2019
6.0	[redacted]	Updated pregnancy language in section 13.5 Updated to v10 of protocol template Updated biostatistician and reviewer Added COVID language to Protocol Compliance Signature Page Added Appendix O – [redacted]	23 September 2020

SYNOPSIS

Protocol Title	Late night study 2: End-of-Day Assessment of Asymptomatic and Symptomatic Soft Lens Wearers
Sponsor	JJVC, 7500 Centurion Parkway, Jacksonville, FL 32256
Clinical Phase	Development phase, Phase 0
Trial Registration	This study will be registered on ClinicalTrials.gov by the Sponsor
Test Article(s)	Investigational Products: Dailies AquaComfort Plus daily disposable contact lenses Acuvue Oasys 1-Day daily disposable contact lenses
Wear and Replacement Schedules	Wear Schedule: daily wear Replacement Schedule: daily disposable

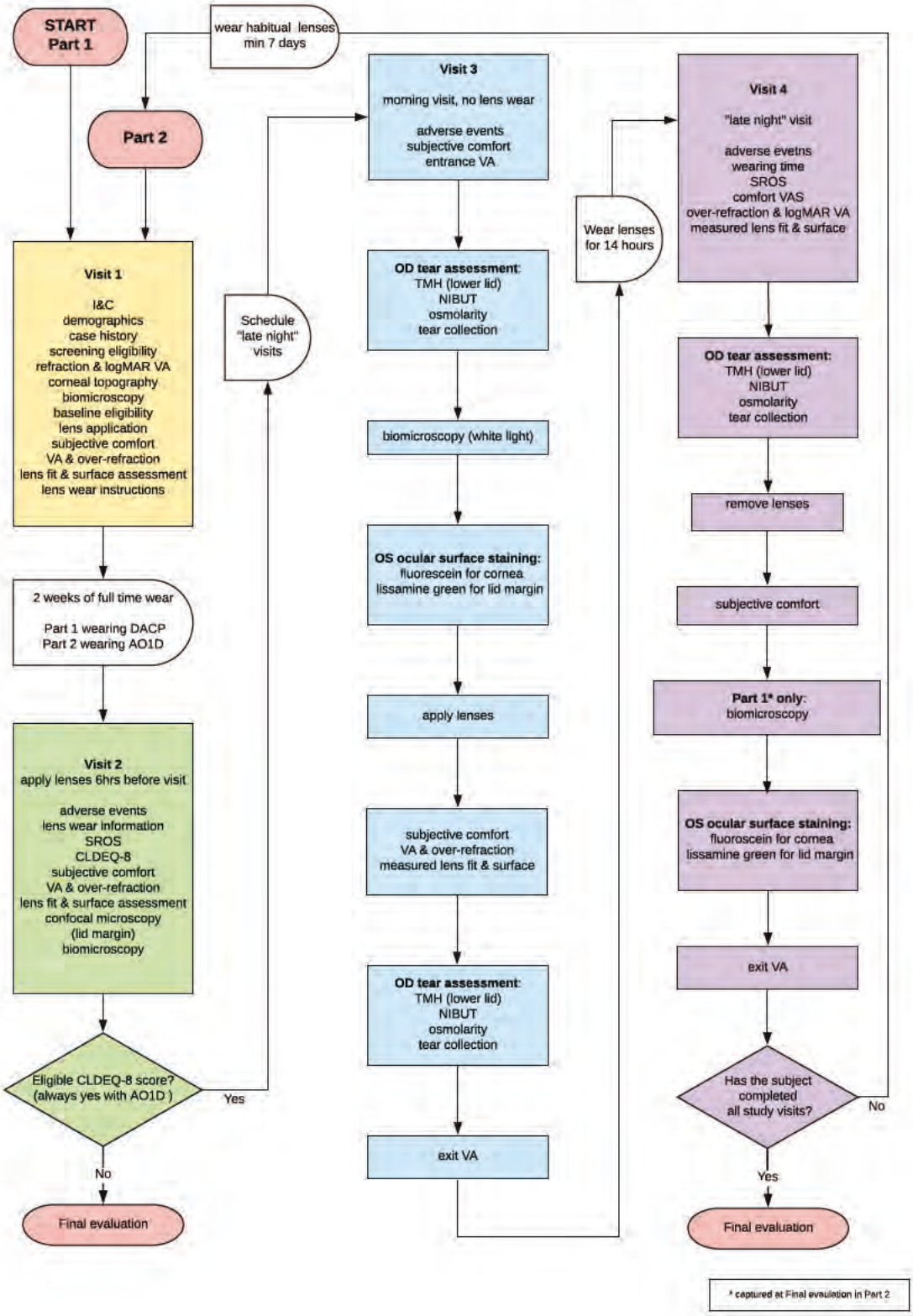
Objectives	Primary Objectives: Part 1: to investigate if there are statistically significant differences in the following clinical measures between asymptomatic and symptomatic contact lens wearers: 1. Upper and lower lid margin lissamine green staining (14 hours) 2. Non-invasive tear break-up time (NIBUT) (14 hours) 3. Tear meniscus height (TMH) (14 hours) 4. Tear film osmolarity (14 hours) 5. Density of white blood cells in the eyelid margins using confocal microscopy (6 hours) *These will be referred to as the 'five clinical measures'* Secondary Objectives: Part 1 and 2: To investigate any possible relationship between subjective scores of contact lens comfort and the five clinical measures. Other Objectives: 1. Part 2*:* to investigate differences in the five clinical measures between asymptomatic and symptomatic contact lens wearers. 2. Part 1 and 2: To investigate if end-of day comfort following lens removal returns to pre-lens wear comfort levels. 3. Part 1 and 2: To provide frozen samples of tear film for further laboratory analysis which will be outlined in separate laboratory protocols. 4. To investigate the relationship between difference in CLDEQ-8 score between Part 1 and 2 and the difference in the five clinical measures between Part 1 and 2. 5. To investigate the relationship between difference in CLDEQ-8 score between Part 1 and 2 and the difference in the (follow-up minus baseline) and (follow-up minus fitting) values between Part 1 and Part 2 for all clinical measures except density of white blood cells. 6. Part 1 and 2: To investigate the change from baseline and fitting in all the clinical measures except density of white blood cells in the eyelid margins for asymptomatic and symptomatic subjects.

Study Endpoints	Primary endpoints: Lid margin staining grade, NIBUT, TMH, tear film osmolarity, mean density of white blood cells Secondary endpoints: VAS comfort scores Other endpoints: Change from baseline, change from fitting, CLDEQ-8 and change in CLDEQ-8
Study Design	This is a 2-Part, 8-Visit, single-center, open-label, bilateral and dispensing clinical study. In Part 1 (Visits 1-4) all subjects will be dispensed Dailies AquaComfort Plus, in Part 2 (Visits 5-8) all subjects will be dispensed Acuvue Oasys 1-Day. Part 1 Approximately 210-240 subjects will be recruited and fitted with Dailies AquaComfort Plus over approximately a two-week period in order to identify ~27 asymptomatic (CLDEQ-8 score less or equal to 10) and ~27 symptomatic (CLDEQ-8 score more than or equal to 20). Only those subjects classified as asymptomatic or symptomatic at the end of Visit 2 (~54 subjects) will be asked to continue. Visits 3 and 4 will take place in the early morning and after 14 ± 2 hours respectively, on a single study day. Part 2 Subjects who complete Part 1 (~ 54 subjects) will continue onto Part 2. The visit procedures will be the same as for Part 1 but subjects will use the Acuvue Oasys 1-Day lens. See the flow chart at the end of the synopsis table for the schematic of the study visits and procedures of main observations (Figure 1)
Sample Size	Part 1, Visits 1 & 2: ~210-240 subjects Part 1, Visits 3 & 4: ~54 subjects Part 2: ~54 subjects
Study Duration	The study will last approximately 18 months and will include a 9-month recruitment period.
Anticipated Study Population	Habitual soft contact lens wearers aged 18-45 years will be stratified into asymptomatic and symptomatic lens wearers based on their CLDEQ-8 score.

Eligibility Criteria	Potential subjects must satisfy all of the criteria listed in Section 3.2 to be enrolled in the study. Inclusion Criteria after Screening 1. They are 18-45 years of age (inclusive). 2. They understand their rights as a research subject and are willing and able to sign a Statement of Informed Consent. 3. They are willing and able to follow the protocol. 4. They agree not to participate in other clinical research while enrolled on this study. 5. They currently use daily disposable soft daily wear contact lenses (worn bilaterally) (within the last six months) which may be spherical, toric or multifocal. 6. They agree to wear their lenses for at least 12-14 hours per day. 7. They own a wearable pair of spectacles (by self report). Inclusion Criteria after Baseline 8. They have a spherical contact lens prescription in the range +6.00 to -10.00 DS (based on the calculated ocular refraction). 9. They have up to a maximum of 1.00 DC of refractive astigmatism (based on the calculated ocular refraction). 10. They have best corrected distance visual acuity of at least 0.20 binocularly. Potential subjects who meet any of the following criteria will be excluded from participating in the study: Exclusion Criteria after Screening: 1. They have an ocular disorder which would normally contra-indicate contact lens wear. 2. They have a systemic disorder which would normally contra-indicate contact lens wear. 3. No ocular topical medications (including comfort drops) from 24 hours prior to study visits or during the wear of any study lenses. 4. They are regularly using anti-inflammatory or pain medications (i.e. medication routinely used more than twice per week). 5. They have had cataract surgery. 6. They have had corneal refractive surgery. 7. They are pregnant or breast-feeding. 8. They have any infectious disease (e.g. hepatitis) or any immunosuppressive disease (e.g. HIV) or a history of anaphylaxis or severe allergic reactions.

	9. They are an employee or immediate family member of an employee of the clinical site (e.g. Investigator, Coordinator, Technician). 10. They have taken part in any other clinical trial or research within two weeks prior to starting this study. 11. History of allergy to sodium fluorescein or lissamine green. Exclusion Criteria after Baseline: 12. They have any corneal distortion e.g. as a result of previous rigid lens wear or have keratoconus. 13. They have any slit lamp findings of Efron Grade 3 or greater (e.g. corneal oedema, corneal neovascularization, tarsal abnormalities, conjunctival injection) or findings of < Grade 3 which in the investigator's opinion would contraindicate contact lens wear.
Disallowed Medications/Interventions	No ocular topical medications (including comfort drops) from 24 hours prior to study visits or during the wear of any study lenses. No systemic medications that in the view of the investigator may affect the ocular surface or contact lens wear from 24 hours prior to study visits. No regular use of anti-inflammatory or pain medications (i.e. medication routinely used more than twice per week).
Measurements and Procedures	Lid margin staining, NIBUT, TMH, tear film osmolarity, VAS comfort score, logMAR VA, lens fitting measurements, white blood cells using confocal microscopy.
Microbiology or Other Laboratory Testing	Tear film cytokine investigations
Study Termination	The occurrence of one or more Unanticipated Adverse Device Effect (UADE), or any SAE where relationship to study agent cannot be ruled out, will result in stopping further dispensing of investigational product.
Ancillary Supplies/ Study-Specific Materials	Any Sponsor-approved saline pods
Principal Investigator(s) and Study Institution(s)/Site(s)	A full list of Principal Investigators, clinical sites, and institutions is kept separately from the Study Protocol and is included in the study Trial Master File.

Figure 1: Study Flowchart (Note: In Part 2, the visits are Visit 5 to Visit 8)



COMMONLY USED ABBREVIATIONS AND DEFINITIONS OF TERMS

ADD	Plus Power Required For Near Use
ADE	Adverse Device Effect
AE	Adverse Event/Adverse Experience
BCVA	Best Corrected Visual Acuity
BSCVA	Best Spectacle Corrected Visual Acuity
CFR	Code of Federal Regulations
CLUE	Contact Lens User Experience
COAS	Complete Ophthalmic Analysis System
COM	Clinical Operations Manager
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Center Thickness
[redacted]	[redacted]
D	Diopter
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
JJVC	Johnson & Johnson Vision Care, Inc.
LC	Limbus Center
LogMAR	Logarithm of Minimal Angle of Resolution
MedDRA©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIBUT	Non-invasive tear break up time
NIH	National Institutes of Health
OD	Right Eye
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
OS	Left Eye
OU	Both Eyes
PD	Protocol Deviation
PHI	Protected Health Information

PI	Principal Investigator
PIG	Patient Instruction Guide
PQC	Product Quality Complaint
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
TMH	Tear meniscus height
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VA	Visual Acuity

1. INTRODUCTION AND BACKGROUND

The study design and the objectives were based on the results obtained through previous clinical work ([redacted][5] and [redacted][6]) which showed that clinical parameters such as lid margin staining, tear film osmolarity, NIBUT, tear meniscus height (TMH) and the appearance of white blood cells in the lid margin are different in asymptomatic and symptomatic soft lens wearers. This study aims to confirm the results obtained and attempts to replicate the previous findings with Dailies AquaComfort Plus (DACP) and then to explore the potential impact on the findings using the same methodology with Acuvue Oasys 1-Day (O1D). Utilizing this approach will allow us to identify the best endpoints to predict end-of-day contact lens discomfort.

1.1. Name and Descriptions of Investigational Products

The products used in this clinical study are:

Dailies AquaComfort Plus (Alcon) daily disposable contact lenses
Acuvue Oasys 1-Day (JJVC) daily disposable contact lenses

Both lenses are CE marked. Further details about the test articles are found in Section 6 of this protocol.

1.2. Intended Use of Investigational Products

The lenses will be used as indicated i.e. for daily wear, daily disposable use. Each lens type will be worn bilaterally for a two-week period and then followed up with an additional single study day. Subjects will be encouraged to wear the lenses for 12-14 hours during the two-week wear period and then for 14 ± 2 hours on the ensuing study single visit day.

Only subjects who are classified as asymptomatic or symptomatic will go on to wear the second lens type (O1D). Asymptomatic subjects are defined as those with a CLDEQ-8 score less or equal to 10 and symptomatic subjects are defined as those with a CLDEQ-8 score of more than or equal to 20.

1.3. Summary of Findings from Nonclinical Studies

Not Applicable – marketed products only.

1.4. Summary of Known Risks and Benefits to Human Subjects

This study will use approved marketed products. The following risks/adverse events can be associated with the use of any marketed contact lens:

- Discomfort, pain, watering or unusual secretions of the eyes
- Redness of the eyes
- Reduced vision and sensitivity to light
- In very rare instances corneal infection, scarring or permanent loss of vision may occur

The key invasive procedures in this work and their associated risks are outlined below:

Confocal microscopy
- Some temporary discomfort on manipulation of the eyelids
- Some temporary discomfort during the procedure itself

Staining of the ocular surface with sodium fluorescein
- Some temporary discomfort on application
- Very rarely, anaphylaxis with topical application

Staining of the lid margins with lissamine green
- Some temporary discomfort on application
- No known cases of anaphylaxis with topical application

There is no direct benefit to the subjects enrolled other than being able to try a lens or lenses that they have not had the opportunity to try before. The information obtained from this study may aid in the development of improved contact lenses in the future.

In order to minimise the likelihood of adverse events, subjects will undergo an ocular examination before and after the clinical investigations. Subjects will also be trained on what to do if they develop ocular discomfort, redness or reduced vision and what to do if they need to be seen outside of the Eurolens Research clinic opening hours.

For the most comprehensive risk and benefit information regarding DACP and O1D refer to the latest version of the package insert of the marketed products (Appendix C).

1.5. Relevant Literature References and Prior Clinical Data Relevant to Proposed Clinical Study

All lenses being investigated in this work are CE marked/approved and marketed products. (APPENDIX C: PACKAGE INSERT (APPROVED PRODUCT).

Two previously completed JJVC clinical study reports:

Navascues-Cornago M. [redacted] *Clinical study report version 1.0: End-of-Day clinical assessment of asymptomatic and symptomatic soft contact lens wearers.* April 6, 2018.

Morgan PB. [redacted] *Clinical study report version 1.0: Confocal microscopy of the eyelid margin as a surrogate for contact lens discomfort.* June 12, 2018.

2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Objectives

Primary Objectives

To investigate if there are statistically significant differences in the following clinical measures between asymptomatic and symptomatic lens wearers:

1. Upper and lower lid margin lissamine staining (14 hours)
2. NIBUT (14 hours)
3. TMH (14 hours)
4. Tear film osmolarity (14 hours)
5. Density of white blood cells in the eyelid margins using confocal microscopy (6 hours)

These will be referred to as the five clinical measures.

Secondary Objective(s)
Part 1 and 2: to investigate any possible relationship between subjective scores of contact lens comfort and the five clinical measures.

Other Objectives

1. Part 2: to investigate differences in the five clinical measures between asymptomatic and symptomatic contact lens wearers

2. Part 1 and 2: to investigate if end-of day comfort following lens removal returns to pre-lens wear comfort levels.

3. Part 1 and 2: to provide frozen samples of tear film for further laboratory analysis which will be outlined in separate laboratory protocols.

4. To investigate the relationship between difference in CLDEQ-8 score between Part 1 and 2 and the difference in the five clinical measures between Part 1 and 2.

5. To investigate the relationship between difference in CLDEQ-8 score between Part 1 and 2 and the difference in the (followup – baseline) and (followup – fitting) values between Part 1 and Part 2 for all the clinical measures except density of white blood cells.

6. Part 1 and 2: to investigate the change from baseline and fitting in all the clinical measures except density of white blood cells in the eyelid margins for asymptomatic and symptomatic subjects.

2.2. Endpoints

Primary Endpoint(s)
The primary endpoints in this study are lid margin lissamine green staining grade, NIBUT, TMH, tear film osmolarity at the beginning and the end of a lens-wearing day (after 14 hours). Additionally, the number of white blood cells in the lid margins after 6 hours of lens wear will be investigated.

Lid margin staining

Lid margin staining of the upper and lower eyelids will be performed in the left eye (OS) only using lissamine green. The staining will be graded both subjectively at the time of the clinic visit and also objectively using automated image analysis software from photographs. Images should be collected as soon as possible for best image quality, and grading can be conducted using a slit lamp or from the images.

For the subjective grading the following will be graded for each eyelid:
Horizontal length of staining
Sagittal width of staining
Average staining grade – this is the average of the horizontal and sagittal grades for each eyelid

A final grade will be calculated which is the average of each eyelid's average staining grade.

For the objective image analysis three metrics of staining will be evaluated; (1) Staining Area, (2) Staining Intensity and (3) Staining thickness

Non-invasive Break-up Time (seconds)
NIBUT will be measured using the Medmont topographer for the right eye (OD) only. Three measurements will be undertaken.

Tear Meniscus Height (mm)
The lower tear meniscus in the right eye (OD) only will be imaged using optical coherence tomography (OCT). Three images will be taken.

Tear Film Osmolarity
Tear film osmolarity will be collected in the right eye (OD) only using the Tearlab (Tearlab Corp.) Two measurements will be collected.

White Blood Cells (mean density of cells)
Images, using Confocal Microscopy will be taken in both eyes for both the upper and lower eyelid in the central lid area. These images will be used to determine the density of inflammatory white blood cells.

Secondary Endpoints
Contact lens comfort will be assessed at the beginning and at the end of day (14 ± 2 hours post lens insertion) using a visual analogue scale (VAS) ranging from 0 – 100, where 0 is uncomfortable and 100 is comfortable.

Other Endpoints
Change from baseline and 14 hours and change from fitting and 14 hours (where appropriate) for the following clinical measures:

- upper and lower lid margin staining
- NIBUT
- TMH
- tear film osmolarity

CLDEQ-8 score and change in CLDEQ-8 score

2.3. Hypotheses

Primary Hypotheses
For Part 1:

1. Symptomatic subjects will have, on average, statistically significantly, greater upper and lower lid margin staining compared to asymptomatic subjects after 14 hours of lens wear.

2. Symptomatic subjects will have, on average, statistically significantly, shorter NIBUT compared to asymptomatic subjects after 14 hours of lens wear.

3. Symptomatic subjects will have, on average, statistically significantly, lower TMH compared to asymptomatic subjects after 14 hours of lens wear.

4. Symptomatic subjects will have, on average, statistically significantly, greater tear film osmolarity compared to asymptomatic subjects after 14 hours of lens wear.

5. Symptomatic subjects will have, on average, statistically significantly, greater density of white blood cells (visualized by confocal microscopy) in both the upper and lower lid margins compared to asymptomatic subjects after 6 hours of lens wear.

Secondary Hypotheses:

For Part 1 and 2

1. There is a statistically significant relationship with at least one of the five clinical measures (lid margin staining, NIBUT, TMH, tear film osmolarity and density of white blood cells) and subjective comfort measured using VAS grading scales at 14 hours (6 hours for white cells).

Other Hypotheses:
For Part 2:

1. Symptomatic subjects will have, on average, statistically significantly, greater upper and lower lid margin staining compared to asymptomatic subjects after 14 hours of lens wear.

2. Symptomatic subjects will have, on average, statistically significantly, shorter NIBUT compared to asymptomatic subjects after 14 hours of lens wear.

3. Symptomatic subjects will have, on average, statistically significantly, lower TMH compared to asymptomatic subjects after 14 hours of lens wear.

4. Symptomatic subjects will have, on average, statistically significantly, greater tear film osmolarity compared to asymptomatic subjects after 14 hours of lens wear.

5. Symptomatic subjects will have, on average, statistically significantly, greater density of white blood cells (visualized by confocal microscopy) in both the upper and lower lid margins compared to asymptomatic subjects after 6 hours of lens wear.

For Part 1 and 2:

1. The measured end of day discomfort score, following lens removal, will not be statistically significantly different than the pre-lens wear discomfort score.

2. There will be a statistically significant relationship between change in CLDEQ score between Part 1 and Part 2 and a change in the five clinical parameters investigated between Part 1 and Part 2.

3. There will be a statistically significant relationship between change in CLDEQ score between Part 1 and Part 2 and the difference in the (follow-up – baseline) and (follow-up – fitting) values between Part 1 and Part 2 for all clinical measures except density of white blood cells.

4. For Part 1 and 2: at 14 hours, symptomatic subjects will have a statistically significantly, greater change from baseline in all the clinical measures except density of white blood cells in the eyelid margins.

Other exploratory analyses may be conducted at the discretion of the study responsible clinician.

3. TARGETED STUDY POPULATION

3.1. General Characteristics

The study population will be healthy contact lens wearers aged 18-45 years of age from a single site in the United Kingdom (UK). Two groups will be recruited: asymptomatic lens wearers reporting a low score on the CLDEQ-8 scale and symptomatic wearers reporting a high score on the same scale. Specific details are provided below.

3.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria after Screening

1. They are 18-45 years of age (inclusive).
2. They understand their rights as a research subject and are willing and able to sign a Statement of Informed Consent.
3. They are willing and able to follow the protocol.
4. They agree not to participate in other clinical research while enrolled on this study.
5. They currently use daily disposable soft daily wear contact lenses (worn bilaterally) (within the last six months) which may be spherical, toric or multifocal.

6. They agree to wear their lenses for at least 12-14 hours per day.
7. They own a wearable pair of spectacles (by self report).

Inclusion Criteria after Baseline

8. They have a spherical contact lens prescription in the range +6.00 to -10.00 DS (based on the calculated ocular refraction).
9. They have up to a maximum of 1.00 DC of refractive astigmatism (based on the calculated ocular refraction).
10. They have best corrected distance visual acuity of at least 0.20 binocularly.

3.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Exclusion Criteria after Screening:

1. They have an ocular disorder which would normally contra-indicate contact lens wear.
2. They have a systemic disorder which would normally contra-indicate contact lens wear.
3. No ocular topical medications (including comfort drops) from 24 hours prior to study visits or during the wear of any study lenses.
4. They are regularly using anti-inflammatory or pain medications (i.e. medication routinely used more than twice per week).
5. They have had cataract surgery.
6. They have had corneal refractive surgery.
7. They are pregnant or breast-feeding.
8. They have any infectious disease (e.g. hepatitis) or any immunosuppressive disease (e.g. HIV) or a history of anaphylaxis or severe allergic reactions.
9. They are an employee or immediate family member of an employee of the clinical site (e.g. Investigator, Coordinator, Technician).
10. They have taken part in any other clinical trial or research within two weeks prior to starting this study.
11. History of allergy to sodium fluorescein or lissamine green.

Exclusion Criteria after Baseline

12. They have any corneal distortion e.g. as a result of previous rigid lens wear or have keratoconus.
13. They have any slit lamp findings of Efron Grade 3 or greater (e.g. corneal oedema, corneal neovascularization, tarsal abnormalities, conjunctival injection) or findings of < Grade 3 which in the investigator's opinion would contraindicate contact lens wear.

3.4. Enrollment Strategy

Study subjects will be recruited from the Institution/clinical site's subject database and/or utilizing Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved materials.

4. STUDY DESIGN AND RATIONALE

4.1. Description of Study Design

PART 1: VISITS 1 AND 2
A single-arm, non-randomised, open-label, bilateral dispensing clinical investigation in which each subject's asymptomatic or symptomatic status will be confirmed based on their CLDEQ-8 after two-weeks of wear of the DACP lens. Subjects with a CLDEQ-8 score less or equal to 10 (classified as asymptomatic) or more than or equal to 20 (classified as symptomatic) will continue. Recruitment will stop when approximately 27 asymptomatic and 27 symptomatic subjects are enrolled onto Part 1, Visit 3 and beyond.

PART 1: VISITS 3 AND 4
This is a single arm study with two different population groups (asymptomatic vs. symptomatic depending on their CLDEQ-8 score) and is a non-randomized, open-label, bilateral dispensing clinical investigation.

All subjects will wear the same lens type (DACP) and will be aware of the lens they are receiving; however, subjects and investigators will be masked to whether participants have been assigned to the asymptomatic or symptomatic group. As far as is logistically possible, each group (asymptomatic and symptomatic) will have a similar ratio of gender distribution among male and female volunteers.

PART 2: VISITS 5 AND 6
This will be a repeat of Part 1, Visits 1 and 2 but will use the O1D lens. Regardless of subjects' classification by the CLDEQ-8, all subjects will move on to Part 2, Visits 7 and 8.

PART 2: VISITS 7 AND 8
This will be a repeat of Part 1, Visits 3 and 4 using the O1D lens. CLDEQ-8 classification with O1D does not affect participation in Part 2.

N.B. If a subject changes their habitual lens type during the study this will not affect their participation in subsequent visits.

4.2. Study Design Rationale

The study utilizes a similar design to what was employed in [redacted]. The purpose of designing the two studies similarly was to allow for a meta-analysis to be performed at a later date.

4.3. Enrollment Target and Study Duration

- The overall target is for 54 subjects to complete Part 2 of the study. Approximately 210-240 eligible subjects will be enrolled for Part 1 (Visits 1 and 2). It will be determined based on Visit 2 results whether subjects are suitable to continue in the study. Once the Informed Consent Form signed the subject will be considered enrolled. A replacement will be enrolled if a subject discontinues from the study before completion.
- Approximately 54 subjects (consisting of approximately 27 asymptomatic and 27 symptomatic subjects) will continue to Part 1, Visit 3 to complete all remaining visits.
- The work will be conducted at a single study site and enrollment is expected to take in the region of 12 months. Each subject will attend either a) two visits (Part 1, Visits 1 and 2) if they are not classified as asymptomatic or symptomatic at the end of Part 1, Visit 2 or b) eight visits (all visits in Parts 1 and 2) if they are successfully classified as asymptomatic or symptomatic at the end of Part 1, Visit 2.

  The study is expected to last for 18 months in total.

5. TEST ARTICLE ALLOCATION AND MASKING

5.1. Test Article Allocation

This is a non-randomized study. All subjects will receive the same lens type to be worn bilaterally in both Part 1 (Dailies AquaComfort Plus) and Part 2 (Acuvue Oasys 1-Day).

5.2. Masking

This is an open label study where the identity of the lenses used is known to all. However, both subjects and investigators involved with data collection will be masked as to which group (asymptomatic or symptomatic) they have been assigned to following Part 1, Visit 2.

Under normal circumstances, the mask should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the mask should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the Investigator may, in an emergency, contact the medical monitor. In the event the mask is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unmasking must be documented in the subject record. The Investigator is also advised not to reveal the study treatment assignment to the clinical site or Sponsor personnel.

Subjects who have had their treatment assignment unmasked are expected to return for all remaining scheduled evaluations. Subjects who are discontinued will be replaced.

5.3. Procedures for Maintaining and Breaking the Masking

Masking of test articles is not applicable.

Masking of the investigators will not be broken unless information concerning the subject's stratum (i.e. asymptomatic or symptomatic) is necessary for the urgent medical treatment of the subject. The Sponsor must be notified before the mask is broken.

6. STUDY INTERVENTION

6.1. Identity of Test Articles

The following contact lenses will be used in this study:

Table 1: Test Articles

	Test 1	Test 2
Name	Dailies AquaComfort Plus	Acuvue Oasys 1-Day
Manufacturer	Alcon	Johnson & Johnson Vision
Compass Protocol(s) and/or Lot Number or Other Identifier	Marketed Product	Marketed Product
Lens Material	nelfilcon A	senofilcon A
Nominal Base Curve @ 22 °C	8.7 mm	8.5 mm 9.0 mm
Nominal Diameter @ 22 °C	14.0 mm	14.3 mm
Nominal Distance Powers (D)	+6.00 to -10.00	+6.00 to -10.00
Oxygen Permeability (Dk)	20	77
Wear Schedule in Current Study	Daily disposable	Daily disposable
Replacement Frequency	Daily	Daily
Packaging Form (vial, blister, etc.)	Blister	Blister

The specific lot numbers for the test articles will be listed on the Clinical Supplies Shipping Report and will be retained in the Investigator Site File and in the TMF.

PART 1, VISITS 1 AND 2
A fitting bank will be ordered to ensure we have the desired lenses at Visit 1. The study site will supply a list of required lenses.

PART 1, VISITS 3 AND 4
Lenses from the fitting bank will be used.

PART 2, VISITS 5 AND 6
A fitting bank will be ordered in order to ensure we have the desired lenses at Visit 5. The 9.0 mm base curve can be ordered in a reduced number of BVPs (e.g. -1.00 to -6.00DS) as these are less likely to be used. The study site will supply a list of required lenses.

PART 2, VISITS 7 AND 8
Lenses from the fitting bank will be used.

6.2. Ancillary Supplies/Products

Table 2: Ancillary Supplies

Product	Saline pods	Fluorescein Strips	Lissamine Green
Manufacturer	Any sponsor-approved manufacturer of sterile, preservative free, single use saline (0.9%w/v sodium chloride solution)	Any sponsor approved product	Contacare Ophthalmics and Diagnostics (or alternative Sponsor-approved product)
Preservative	None	None	None
Other distinguishing items (dye, packaging, approval status, etc.	N/A		

6.3. Administration of Test Articles

Test articles will be dispensed to subject meeting all eligibility requirements, including any dispensing requirements set forth in this clinical protocol. Subjects will be dispensed an adequate supply of test articles to complete the study. Lost or damaged test articles may be replaced at the discretion of the Investigator and/or the Sponsor.

6.4. Packaging and Labeling

The test articles will be packaged in blisters as the primary packaging. The test articles will be in in plastic bags as the secondary packaging form. In this open label study, no additional primary label is required.

6.5. Storage Conditions

Test articles will be maintained at ambient temperatures at the clinical site. Test articles must be kept under secure conditions.

6.6. Collection and Storage of Samples

When possible, any lens or test article associated with an Adverse Events and/or a Product Quality Complaint must be retained and stored in a glass vial with moderate solution pending directions from the sponsor for potential return back to JJVC.

Tear samples will be frozen for subsequent analysis. Samples will initially be stored at -20 °C but will be transferred (using dry ice) to a -80°C freezer within three working days.

6.7. Accountability of Test Articles

JJVC will provide the Investigator with sufficient quantities of study articles and supplies to complete the investigation. The Investigator is asked to retain all lens shipment documentation for the test article accountability records.

Test article must be kept in a locked storage cabinet, accessible only to those assigned by the Investigator for dispensing. The Investigator may delegate this activity to authorized study site personnel listed on the Site Delegation Log. All test articles must be accounted. This includes:

1. What was dispensed for the subject for trial fitting, to wear out of the office, or issued for the subject to replace appropriately between visits
2. What was returned to the Investigator unused
3. The number and reason for unplanned replacements

The Investigator will collect all unused test articles from the subjects at the end of the subject's participation. Subject returned unused test articles must be separated from the clinical study inventory of un-dispensed test articles, and must be labeled with the subject number and date of return. Following final reconciliation of test articles by the monitor, the Investigator or monitor will destroy all unused test articles unless the Sponsor requires another course of action.

If there is a discrepancy between the shipment documents and the contents, contact the study monitor immediately.

Reference [redacted]: Site Instructions for Test Article Receipt and Test Article Accountability for additional information.

7. STUDY EVALUATIONS

7.1. Time and Event Schedule

Table 3: Time and Events

PART 1				
Visit	1	2	3	4
	Screening, Baseline, Treatment 1	Treatment 1 Follow-up	Treatment 2	Treatment 2 Follow-up
Time Point		14 ± 3 days from Visit 1 6±1 hours lens wear on visit day	2 to 180 days from Visit 2	14 ± 2 hours from Visit 3
Estimated Visit Duration	1.5 hours	1.5 hours	3.0 hours	2.0 hours
Statement of Informed Consent/Privacy statement	X			
Demographics	X			
Medical History/Concomitant Medications	X	X	X	X
Habitual Contact Lens Information	X			
Inclusion/Exclusion Criteria	X			
Adverse event review		X	X	X
Subjective Sphero-Cylindrical Refraction	X			
Visual acuity with refraction	X			
Corneal topography	X			
Tear meniscus height			X	X
Non-invasive tear break-up time			X	X
Tear film osmolarity			X	X
Tear sample collection (and storage)			X	X
Slit Lamp biomicroscopy	X	X	X	X
Compliance		X		X
Continuance	X	X	X	
Lid margin staining and photography			X	X
Lens application	X		X	
Comfort scores	X	X	X	X

Over Refraction (with lenses)	X	X	X	X
Lens fit/surface assessment	X	X	X	X
Dispense investigational product	X		X	
Patient completed questionnaire (CLDEQ-8)		X		
Confocal microscopy		X		
Visual acuity	X	X	X	X

PART 2				
Visit	5	6	7	8
	Screening, Baseline, Treatment 3	Treatment 3 Follow-up	Treatment 4	Treatment 4 Follow-up
Time Point	9 to 90 days from Visit 4	14 ± 3 days from Visit 5 6±1 hours lens wear on visit day	2 to 180 days from Visit 6	14 ± 2 hours from Visit 7
Estimated Visit Duration	1.5 hours	1.5 hours	3.0 hours	2.0 hours
Medical History/Concomitant Medications	X	X	X	X
Habitual Contact Lens Information	X			
Adverse event review	X	X	X	X
Tear meniscus height			X	x
Non-invasive tear break-up time			X	X
Tear film osmolarity			X	X
Tear sample collection (and storage)			X	X
Slit Lamp biomicroscopy	X	X	X	X
Compliance		X		X

PART 2				
Visit	5	6	7	8
	Screening, Baseline, Treatment 3	Treatment 3 Follow-up	Treatment 4	Treatment 4 Follow-up
Time Point	9 to 90 days from Visit 4	14 ± 3 days from Visit 5 6±1 hours lens wear on visit day	2 to 180 days from Visit 6	14 ± 2 hours from Visit 7
Estimated Visit Duration	1.5 hours	1.5 hours	3.0 hours	2.0 hours
Continuance	X		X	
Lid margin staining and photography			X	X
Lens application	X		X	
Comfort scores	X	X	X	X
Over Refraction (with lenses)	X	X	X	X
Lens fit/surface assessment	X	X	X	X
Dispense investigational product	X		X	
Patient completed questionnaire (CLDEQ-8)		X		
Confocal microscopy		X		
Visual acuity	X	X	X	X

7.2. Detailed Study Procedures

PART 1, VISIT 1

Subjects should be asked to attend Visit 1 without their habitual lenses *in situ*. If possible subjects should not wear lenses for 24 hours prior to the study visit in order to reduce the risk of biomicroscopic signs being a cause of exclusion to entering the study.

The visit can still go ahead if the subject is wearing their habitual lenses and it can take place at any time of the working day.

Visit 1: Screening			
Step	Procedure	Details	[redacted]
1.1	Statement of Informed Consent	Each subject must read, understand, and sign the Statement of Informed Consent before being enrolled into the study. The Principal Investigator or his/her designee conducting the informed consent discussion must also sign the consent form. **Note**: The subject must be provided a signed copy of this document.	
1.2	Demographics	Record the subject's year of birth and age, gender, race and ethnicity.	
1.3	Medical History and Concomitant Medications	Questions regarding the subjects' medical history and concomitant medications.	
1.4	Habitual Lenses	Questions regarding the subject's habitual lens type and parameters.	
1.5	Eligibility after Screening	All responses to Screening Inclusion Criteria questions must be answered "yes" and all responses to Exclusion Criteria must be answered "no" for the subject to be considered eligible. *If a subject is deemed to be ineligible after screening, proceed to the Final Evaluation and complete the Subject Disposition. Refraction and Biomicroscopy forms are not required.*	
Visit 1: Baseline			
Step	Procedure	Details	[redacted]
1.6	Subjective sphero-cylindrical refraction	Subjective sphero-cylindrical refraction will be performed on both eyes	

Visit 1: Baseline			
Step	Procedure	Details	[redacted]
1.7	LogMAR visual acuity	Distance high contrast visual acuity will be measured OD,OS and OU with the subjective refraction in place.	Eurolens Research SOP # 12a
1.8	Corneal topography	Corneal topography using the Medmont topographer will be carried out on each eye. Simulated K readings (mm) will be documented.	Eurolens Research SOP # 16
1.9	Slit lamp biomicroscopy	Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales. If any slit lamp findings are Efron Grade 3 or greater (e.g. corneal edema, corneal neovascularization, tarsal abnormalities, conjunctival injection) or < Efron Grade 3 which in the investigator's opinion would contraindicate contact lens wear, the subject may not continue at this time.	Eurolens Research SOP #13
1.10	Eligibility after baseline	All responses to Inclusion Criteria questions must be answered "yes" and all responses to Exclusion Criteria questions must be answered "no" for the subject to be considered eligible. *If subject is deemed to be ineligible after baseline, proceed to Final Evaluation and complete all forms.* If in the opinion of the investigator the subject may be eligible at a later date, the subject may be brought in for up to ONE additional visit of this type.	

Visit 1: Treatment 1 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
1.11	Lens application	A Dailies AquaComfort Plus contact lens will be applied to each eye. BVP and lot number will be recorded. If a lens is damaged, a Product Quality Complaint Form will be completed. The lens will be stored in a labeled vial with unpreserved saline, and clearly differentiated from any other lenses.	

Visit 1: Treatment 1 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
		Lenses will settle for approximately 5 minutes	
1.12	Lens fitting and surface assessment	Lens fit will be recorded for each of the following criteria: horizontal centration, vertical centration, movement and coverage. The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research Grading Scale (lens fit and surface assessment)
1.13	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye as well as binocularly before and after over-refraction. If there is an over-refraction of +/- 0.50DS or more, the lenses would usually be changed. However, the final decision on this will rest with the investigator. Up to TWO power modifications are allowed. N.B Minimum acceptable logMAR VA is 0.18 binocularly.	Eurolens Research SOP # 12a
1.14	Subjective comfort	Subjective comfort scores for each lens (OD and OS) separately using a vertical VAS scale will be recorded.	[redacted]
1.15	Continuance	The lens fit and VA must be acceptable in order for a subject to be dispensed lenses. *Since no other base curves are available, if the lens fit is deemed to be inadequate the subject should be exited from the study.* Minimum acceptable logMAR VA is 0.18 binocularly *If subject is deemed to be ineligible after baseline, proceed to Final Evaluation and complete all forms.*	
1.16	Dispense lenses	The subject will be instructed to wear the lenses on a daily disposable basis and informed that no other products should be used until the next study visit. Subjects will be	

Visit 1: Treatment 1 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
		instructed to wear their lenses for at least 5 days per week for about 12 hours per day before the next visit. A patient instruction guide will be issued. Subjects should also be instructed to return any unopened lenses to the investigator at the next visit. Subjects do not need to keep any worn lenses.	
1.17	End of Visit 1 and Instructions	Subject discharged and asked to return two weeks later, having worn the study lenses for 6 ±1 hours that day.	

PART 1, VISIT 2

Subjects will be asked to attend Visit 2 wearing the study lenses. The visit should take place 6 ± 1 hours after the subject applied their lenses on the visit day.

Visit 2: Treatment 1 Follow-Up (after two weeks)			
Step	Procedure	Details	[redacted]
2.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
2.2	Wearing Time	Record the wearing time on the day of the visit as well as the average wearing time and comfortable wearing time since the last visit.	
2.3	Compliance	Ensure the subject has been wearing lenses for 6 ± 1 hours. If the subject has not been complaint with wearing time, the subject can be asked to return on ONE more occasion.	
2.4	Subject Reported Ocular Symptoms	Record subject reported ocular symptoms.	[redacted]
2.5	Collection of unopened study lenses	The investigator will collect any unopened lenses.	
2.6	CLDEQ-8	Subjects will complete the CLDEQ-8 questionnaire (Investigator masked).	

Visit 2: Treatment 1 Follow-Up (after two weeks)			
Step	Procedure	Details	[redacted]
2.7	Subjective comfort	Subjective comfort scores using a vertical VAS scale will be recorded for the following for each lens (OD and OS): Comfort just after lens application over the two week period Comfort just before lens removal over the two week period	[redacted]
2.8	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye and binocularly before and after over-refraction.	Eurolens Research SOP # 12a
2.9	Lens fitting and surface assessment	Lens fit will be recorded for each of the following criteria: horizontal centration, vertical centration, movement and coverage. The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research Grading Scale (lens fit and surface assessment)
2.10	Lens removal	Lenses will be removed and discarded.	
2.11	Confocal microscopy (ONLY subjects who are classified as asymptomatic or symptomatic)	Confocal microscopy will be undertaken in the following areas: OD and OS Central upper lid margin OD and OS Central lower lid margin A number of images will be undertaken across the central lid area. Image analysis will be subsequently undertaken in order to determine the number of white blood cells.	Eurolens Research SOP #53
2.12	Slit lamp biomicroscopy	Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales. N.B. For subjects who are NOT classified as asymptomatic or symptomatic slit lamp biomicroscopy will take place as part of the final evaluation form.	Eurolens Research SOP #13
2.13	Continuance	For a subject to continue on the study they must meet the following criteria: Their CLDEQ-8 score must be either ≤10 (to be classified as asymptomatic)	

Visit 2: Treatment 1 Follow-Up (after two weeks)			
Step	Procedure	Details	[redacted]
		or ≥ 20 (to be classified as symptomatic). Subjects who discontinue from the study at this stage should complete an exit form (a copy is given) as well as a final evaluation form. Reimbursement issued for discontinuing subjects.	
2.14	Exit Visual Acuity	Record distance high contrast logMAR visual acuity (OD, OS and OU) with their with their refractive correction from Part 1, Visit 1 (or habitual spectacles) in place.	Eurolens Research SOP # 12a
2.15	End of Visit 2 and Instructions	Continuing subjects will be asked to return for Visit 3 between 2 and 180 days after Visit 2, and may resume use of their habitual contact lenses until then. Subjects should be asked NOT to wear their lenses to Visit 3.	

PART 1, VISIT 3

Visit 3 will take place in the morning and subjects MUST attend without lenses *in situ*. If possible subjects should not wear lenses for 24 hours prior to the study visit in order to reduce the risk of biomicroscopic signs being a cause of being unable to continue on the study.

If subjects attend wearing their own lenses, this visit should NOT go ahead. The visit can still go ahead if the subject has worn their habitual lenses in the 24 hours prior to the visit.

Visit 3: Baseline			
Step	Procedure	Details	[redacted]
3.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
3.2	Subjective comfort	Subjective comfort scores using a vertical VAS scale will be recorded for each eye separately before lens application.	[redacted]
3.3	Entrance Visual Acuity	Record distance high contrast LogMAR visual acuity (OD, OS and OU) with their refractive correction from Part 1, Visit 1 (or habitual spectacles), in place.	Eurolens Research SOP # 12a

Visit 3: Baseline			
Step	Procedure	Details	[redacted]
3.4	Tear meniscus height	The OD lower tear meniscus will be imaged using the OCT. Three images will be taken.	Eurolens Research SOP # 58
3.5	Non-invasive tear break-up time	OD tear film break up time will be measured using the Medmont topographer Three measurements will be undertaken.	Eurolens Research SOP # 16
3.6	Tear film osmolarity	OD osmolarity measured using the Tearlab. Two measurements will be undertaken.	Eurolens Research SOP # 52
3.7	Tear sample collection	OD; 2µl tear sample will be collected using a capillary glass tube before application of any dyes to the ocular surface. Tears will be collected over a maximum period of 15 minutes.	Eurolens Research SOP # 57
3.8	Slit lamp biomicroscopy (white light only)	Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales for both eyes. **OS:** NO LID EVERSION	Eurolens Research SOP #13
3.9	Continuance	If any slit lamp findings are Efron Grade 3 or greater (e.g. corneal oedema, corneal neovascularization, tarsal abnormalities, conjunctival injection) or < Efron Grade 3 which in the investigator's opinion would contraindicate contact lens wear, the subject may not continue at this time. If in the opinion of the investigator the subject may be eligible at a later date, the subject may be brought in for up to ONE additional visit of this type.	

Visit 3: Treatment 2 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
3.10	Ocular surface and lid margin staining photography and grading	OS ONLY: Sodium fluorescein will be added to the ocular surface and the following will be graded using Efron scales: corneal and bulbar conjunctival staining.	Eurolens Research SOP #13

Visit 3: Treatment 2 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
		OS ONLY: Lissamine green will then be added to the ocular surface and photographs of the upper and lower lid margin staining will be taken. These images will be used to subjectively grade lid margin staining at the time of the visit and for subsequent automated image analysis. OS: after all lissamine green assessments have been completed, the eyelid will be everted and the palpebral conjunctiva will be graded using Efron Grading scales.	Eurolens Research SOP #41
3.11	Lens application	A Dailies AquaComfort Plus contact lens will be applied to each eye (lens selection based on BVP worn between Visits 1-2). BVP and lot number will be recorded. If a lens is damaged, a Product Quality Complaint Form will be completed. The lens will be stored in a labeled vial with unpreserved saline, and clearly differentiated from any other lenses. Lenses will settle for 5 minutes	
3.12	Subjective comfort	Subjective comfort scores for each lens (OD and OS) separately using a vertical VAS scale will be recorded.	[redacted]
3.13	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye and binocularly before and after over-refraction. The acuity will be recorded to the nearest letter for each eye. If there is an over-refraction of +/- 0.50DS or more, the lenses would usually be changed. However, the final decision on this will rest with the investigator. Up to TWO power modifications are allowed. If the lens is changed, the lens application, comfort and VA steps should be repeated. N.B. Minimum acceptable logMAR VA is 0.18 binocularly.	Eurolens Research SOP # 12a

Visit 3: Treatment 2 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
3.14	Lens fitting and surface assessment	Lens fit will be measured using a slit lamp graticule for the following: **Coverage:** Nasal coverage Temporal Coverage Inferior Coverage Superior Coverage **Centration:** Horizontal centration (by auto calculation) Vertical centration (by auto calculation) **Movement** in primary position The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research SOP # 24 Eurolens Research Grading Scale (surface assessment)
3.15	Tear meniscus height	The OD lower tear meniscus will be imaged using the OCT. Three images will be taken.	Eurolens Research SOP # 58
3.16	Non-invasive tear break-up time	OD tear film break up time will be measured using the Medmont topographer Three measurements will be undertaken.	Eurolens Research SOP # 16
3.17	Tear film osmolarity	OD osmolarity measured using the Tearlab. Two measurements will be undertaken.	Eurolens Research SOP # 52
3.18	Tear sample collection	OD; 2µl tear sample will be collected using a capillary glass tube before application of any dyes to the ocular surface. Tears will be collected over a maximum period of 15 minutes.	Eurolens Research SOP # 57
3.19	LogMAR visual acuity	Distance high contrast visual acuity will be measured for each eye and binocularly. The acuity will be recorded to the nearest letter for each eye.	Eurolens Research SOP # 12a

Visit 3: Treatment 2 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
3.20	Dispensing criteria	The lens fit and VA must be acceptable in order for a subject to be able to continue on the study. *Since no other base curves are available, if the lens fit is deemed to be inadequate the subject should be exited from the study.* Minimum acceptable logMAR VA is 0.18 binocularly *If subject is deemed to be unable to continue, proceed to the Final Evaluation and complete all forms.*	
3.21	Lens wear instructions	The subject will be instructed to wear the lenses for the rest of the day and not to remove the lenses before the next visit.	
3.22	End of Visit 3 and Instructions	Subject discharged and asked to return 14 ± 2 hours later (from the time of lens application).	

PART 1, VISIT 4

Subjects should attend Visit 4 wearing the study lenses which were applied at Visit 3 after 14 ± 2 hours. This is the final visit of Part 1.

Visit 4: Treatment 2 Follow-Up (after 14h)			
Step	Procedure	Details	[redacted]
4.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
4.2	Compliance	Questions regarding the subject's contact lens wear since the previous visit. The number of hours of lens wear, as well as the number of comfortable hours of lens wear will be recorded. N.B. Subjects should <u>not</u> have removed the lenses since the previous visit. If subjects have had to remove one or both lenses, the investigator should stop the visit at	

Visit 4: Treatment 2 Follow-Up (after 14h)			
Step	Procedure	Details	[redacted]
		this point and a Final Evaluation form should be completed. All subjects are eligible to repeat Visits 3 and 4 of Part 1 on ONE more occasion on a different day if any problems with the lens wear occur between Part 1, Visits 3 and 4. If such problems do occur, Visit 3 will also need to be repeated.	
4.3	Subject Reported Ocular Symptoms	Record subject reported ocular symptoms.	
4.4	Subjective comfort	Subjective comfort scores for each lens (OD and OS) separately using a vertical VAS scale will be recorded.	[redacted]
4.5	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye and binocularly as well as after an over-refraction. The acuity will be recorded to the nearest letter.	Eurolens Research SOP # 12a
4.6	Lens fitting and surface assessment	Lens fit will be measured using a slit lamp graticule for the following: **Coverage:** Nasal coverage Temporal Coverage Inferior Coverage Superior Coverage **Centration:** Horizontal centration (by auto calculation) Vertical centration (by auto calculation) **Movement** in primary position The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research SOP # 24 Eurolens Research Grading Scale (surface assessment)
4.7	Tear meniscus height	The OD lower tear meniscus will be imaged using the OCT. Three images will be taken.	Eurolens Research SOP # 58

Visit 4: Treatment 2 Follow-Up (after 14h)			
Step	Procedure	Details	[redacted]
4.8	Non-invasive tear break-up time	OD tear film break up time will be measured using the Medmont topographer Three measurements will be undertaken.	Eurolens Research SOP # 16
4.9	Tear film osmolarity	OD osmolarity measured using the Tearlab. Two measurements will be undertaken.	Eurolens Research SOP # 52
4.10	Tear sample collection	OD; 2µl tear sample will be collected using a glass capillary tube before application of any dyes to the ocular surface. Tears will be collected over a maximum period of 15 minutes.	Eurolens Research SOP # 57
4.11	Lens removal	Lenses will be removed and discarded.	
4.12	Subjective comfort	Subjective comfort scores using a vertical VAS scale will be recorded for each eye separately.	[redacted]
4.13	Slit lamp biomicroscopy	OD: Full biomicroscopy. Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales for both eyes. OS: white light exam only. NO LID EVERSION	Eurolens Research SOP #13
4.14	Ocular surface and lid margin staining photography and grading	OS: Sodium fluorescein will be added to the ocular surface and the following will be graded using Efron scales: corneal and bulbar conjunctival staining. OS ONLY: Lissamine green will then be added to the ocular surface and photographs of the upper and lower lid margin staining will be taken. These images will be used to subjectively grade lid margin staining at the time of the visit and for subsequent automated image analysis. OS: after all lissamine green assessments have been completed, the eyelid will be everted and the palpebral conjunctiva will be graded using Efron Grading scales.	Eurolens Research SOP #13 Eurolens Research SOP #41

Visit 4: Treatment 2 Follow-Up (after 14h)			
Step	Procedure	Details	[redacted]
4.15	Exit Visual Acuity	Record distance high contrast LogMAR visual acuity (OD, OS and OU) with their with their refractive correction from Part 1, Visit 1 (or habitual spectacles) in place.	Eurolens Research SOP # 12a
4.16	End of Visit 4 and instructions	Part 1 complete. Subjects will be asked to return for Part 2 between 9-90 days later. Subjects must return to their habitual lenses for at least 7 days (and ideally have a period of 24 hours without lenses) before going ahead with the next study visit.	

PART 2, VISIT 5

Subjects must have returned to their habitual lenses for at least 7 days prior to taking part in Part 2. Subjects should also be asked to attend this visit without their habitual lenses *in situ*. If possible subjects should not wear lenses for 24 hours prior to the study visit in order to reduce the risk of biomicroscopic signs being a cause of exclusion to continuing on the study.
The visit can still go ahead if the subject is wearing their habitual lenses and can take place at any time of the working day.

Visit 5: Treatment 3 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
5.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
5.2	Entrance Visual Acuity	Record distance high contrast LogMAR visual acuity (OD, OS and OU) with their refractive correction from Part 1, Visit 1 (or habitual spectacles), in place.	Eurolens Research SOP # 12a
5.3	Slit lamp biomicroscopy	Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales.	Eurolens Research SOP #13
5.4	Continuance	If any slit lamp findings are Efron Grade 3 or greater (e.g. corneal oedema, corneal neovascularization, tarsal abnormalities, conjunctival injection) or < Efron Grade 3 which in the investigator's opinion would contraindicate contact lens wear, the subject may not continue at this time.	

Visit 5: Treatment 3 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
		If in the opinion of the investigator the subject may be eligible at a later date, the subject may be brought in for up to ONE additional visit of this type.	
5.5	Lens application	An Acuvue Oasys 1-Day contact lens (8.5 mm base curve) will be applied to each eye. BVP and lot number will be recorded. If a lens is damaged, a Product Quality Complaint Form will be completed. The lens will be stored in a labeled vial with unpreserved saline, and clearly differentiated from any other lenses. Lenses will settle for 5 minutes	
5.6	Lens fitting and surface assessment	Lens fit will be recorded according to a -2 to +2 integer scale for each of the following criteria: horizontal centration, vertical centration, movement and coverage. The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4). If the investigator feels that an 9.0 mm base curve lens would provide a better fit, the lens may be changed. If the lens is changed to an 9.0 mm base curve, then the comfort, VA and over-refraction and lens fit assessment should be repeated.	Eurolens Research Grading Scale (lens fit and surface assessment)
5.7	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye as well as binocularly before and after over-refraction. If there is an over-refraction of +/- 0.50DS or more, the lenses would usually be changed. However, the final decision on this will rest with the investigator. Up to TWO power modifications are allowed.	Eurolens Research SOP # 12a

Visit 5: Treatment 3 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
		Any new lens should be allowed to settle for 5 minutes before comfort is recorded.	
5.8	Subjective comfort	Subjective comfort scores for each lens (OD and OS) separately using a vertical VAS scale will be recorded.	[redacted]
5.9	Continuance	The lens fit and VA must be acceptable in order for a subject to be considered eligible. N.B Minimum acceptable logMAR VA is 0.18 binocularly. *If subject is deemed to be ineligible after baseline, proceed to Final Evaluation and complete all forms.*	
5.10	Dispense lenses	The subject will be instructed to wear the lenses on a daily disposable basis and informed that no other products should be used until the next study visit. Subjects will be instructed to wear their lenses for at least 5 days per week for about 12 hours per day before the next visit. A patient instruction guide will be issued. Subjects should also be instructed to return any unopened lenses to the investigator at the next visit. Subjects do not need to keep any worn lenses.	
5.11	End of Visit 5 and Instructions	Subject discharged and asked to return two weeks later, having worn the study lenses for 6 ±1 hours that day.	

PART 2, VISIT 6

Subjects will be asked to attend Visit 6 wearing the study lenses. The visit should take place 6 ± 1 hours after the subject applied their lenses on the visit day.

Visit 6: Treatment 3 Follow-Up (after two weeks)			
Step	Procedure	Details	[redacted]
6.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	

Visit 6: Treatment 3 Follow-Up (after two weeks)			
Step	Procedure	Details	[redacted]
6.2	Wearing Time	Record the wearing time on the day of the visit as well as the average wearing time and comfortable wearing time since the last visit.	
6.3	Compliance	Ensure the subject has been wearing lenses for 6 ± 1 hours. If the subject has not been complaint with wearing time, the subject can be asked to return on ONE more occasion.	
6.4	Subject Reported Ocular Symptoms	Record subject reported ocular symptoms.	[redacted]
6.5	Collection of unopened study lenses	The investigator will collect any unopened lenses.	
6.6	CLDEQ-8	Subjects will complete the CLDEQ-8 questionnaire.	[redacted]
6.7	Subjective comfort	Subjective comfort scores using a vertical VAS scale will be recorded for the following for each lens (OD and OS): Comfort just after lens application over the two week period Comfort just before lens removal over the two week period	[redacted]
6.8	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye and binocularly before and after over-refraction. The acuity will be recorded to the nearest letter.	Eurolens Research SOP # 12a
6.9	Lens fitting and surface assessment	Lens fit will be recorded for each of the following criteria: horizontal centration, vertical centration, movement and coverage. The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research Grading Scale (lens fit and surface assessment)
6.10	Lens removal	Lenses will be removed and discarded.	

Visit 6: Treatment 3 Follow-Up (after two weeks)			
Step	Procedure	Details	[redacted]
6.11	Confocal microscopy	Confocal microscopy will be undertaken in the following areas: OD and OS Central upper lid margin OD and OS Central lower lid margin A number of images will be undertaken across the central lid area. Image analysis will be subsequently undertaken in order to determine the number of white blood cells. N.B. This will only occur for subjects who are classified as asymptomatic or symptomatic with the CLDEQ-8.	Eurolens Research SOP #53
6.12	Slit lamp biomicroscopy	Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales.	Eurolens Research SOP #13
6.13	Exit Visual Acuity	Record distance high contrast LogMAR visual acuity (OD, OS and OU) with their with their refractive correction from Part 1, Visit 1 (or habitual spectacles) in place.	Eurolens Research SOP # 12a
6.14	End of Visit 6 and Instructions	Subjects will be asked to return for Visit 7 between 2 and 180 days from Visit 6, and may resume use of their habitual contact lenses until then. Subjects should be asked NOT to wear their lenses to Visit 7.	

PART 2, VISIT 7

Visit 7 will take place in the morning and subjects MUST attend without lenses *in situ*. If possible, subjects should not wear lenses for 24 hours prior to the study visit in order to reduce the risk of biomicroscopic signs being a cause of being unable to continue on the study.

If subjects attend wearing their own lenses, this visit should NOT go ahead. The visit can still go ahead if the subject has worn their habitual lenses in the 24 hours prior to the visit.

Visit 7: Baseline			
Step	Procedure	Details	[redacted]
7.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	

Visit 7: Baseline			
Step	Procedure	Details	[redacted]
7.2	Subjective comfort	Subjective comfort scores using a vertical VAS scale will be recorded for each eye separately before lens application.	[redacted]
7.3	Entrance Visual Acuity	Record distance high contrast LogMAR visual acuity (OD, OS and OU) with their refractive correction from Part 1 (or habitual spectacles), Visit 1 in place.	Eurolens Research SOP # 12a
7.4	Tear meniscus height	The OD lower tear meniscus will be imaged using the OCT. Three images will be taken.	Eurolens Research SOP # 58
7.5	Non-invasive tear break-up time	OD tear film break up time will be measured using the Medmont topographer Three measurements will be undertaken.	Eurolens Research SOP # 16
7.6	Tear film osmolarity	OD osmolarity measured using the Tearlab. Two measurements will be undertaken.	Eurolens Research SOP # 52
7.7	Tear sample collection	OD; 2µl tear sample will be collected using a glass capillary tube before application of any dyes to the ocular surface. Tears will be collected over a maximum period of 15 minutes.	Eurolens Research SOP # 57
7.8	Slit lamp biomicroscopy (white light only)	Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales for both eyes. **OS:** NO LID EVERSION	Eurolens Research SOP #13
7.9	Continuance	If any slit lamp findings are Efron Grade 3 or greater (e.g. corneal oedema, corneal neovascularization, tarsal abnormalities, conjunctival injection) or < Efron Grade 3 which in the investigator's opinion would contraindicate contact lens wear, the subject may not continue at this time. If in the opinion of the investigator the subject may be eligible at a later date, the subject may	

Visit 7: Baseline			
Step	Procedure	Details	[redacted]
		be brought in for up to ONE additional visit of this type.	

Visit 7: Treatment 4 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
7.10	Ocular surface and lid margin staining photography and grading	OS ONLY: Sodium fluorescein will be added to the ocular surface and the following will be graded using Efron scales: corneal and bulbar conjunctival staining. OS ONLY: Lissamine green will then be added to the ocular surface and photographs of the upper and lower lid margin staining will be taken. These images will be used to subjectively grade lid margin staining at the time of the visit and for subsequent automated image analysis. OS: after all lissamine green assessments have been completed, the eyelid will be everted and the palpebral conjunctiva will be graded using Efron Grading scales.	Eurolens Research SOP #13 Eurolens Research SOP #41
7.11	Lens application	An Acuvue Oasys 1-Day contact lens will be applied to each eye (lens selection based on BVP/base curve worn between Part 2, Visits 1-2). BVP and lot number will be recorded. If a lens is damaged, a Product Quality Complaint Form will be completed. The lens will be stored in a labeled vial with unpreserved saline, and clearly differentiated from any other lenses. Lenses will settle for 5 minutes	
7.12	Subjective comfort	Subjective comfort scores for each lens (OD and OS) separately using a vertical VAS scale will be recorded.	[redacted]
7.13	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye and binocularly before and after over-refraction. The acuity will be recorded to the nearest letter for each eye.	Eurolens Research SOP # 12a

Visit 7: Treatment 4 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
		If there is an over-refraction of 0.50DS or more, the lenses would usually be changed. However, the final decision on this will rest with the investigator. Up to TWO power modifications are allowed. If the lens is changed, the lens application, comfort and VA steps should be repeated. Any new lens should be allowed to settle for 5 minutes before comfort is recorded. N.B. Minimum acceptable logMAR VA is 0.18 binocularly.	
7.14	Lens fitting and surface assessment	Lens fit will be measured using a slit lamp graticule for the following: **Coverage:** Nasal coverage Temporal Coverage Inferior Coverage Superior Coverage **Centration:** Horizontal centration (by auto calculation) Vertical centration (by auto calculation) **Movement** in primary position The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research SOP # 24 Eurolens Research Grading Scale (surface assessment)

Visit 7: Treatment 4 Lens Fitting and dispensing			
Step	Procedure	Details	[redacted]
7.15	Continuance	The lens fit and VA must be acceptable in order for a subject to continue on the study. Minimum acceptable logMAR VA is 0.18 binocularly *If subject is deemed not to be able to continue, proceed to Final Evaluation and complete all forms.*	
7.16	Tear meniscus height	The OD lower tear meniscus will be imaged using the OCT. Three images will be taken.	Eurolens Research SOP # 58
7.17	Non-invasive tear break-up time	OD tear film break up time will be measured using the Medmont topographer Three measurements will be undertaken.	Eurolens Research SOP # 16
7.18	Tear film osmolarity	OD osmolarity measured using the Tearlab. Two measurements will be undertaken.	Eurolens Research SOP # 52
7.19	Tear sample collection	OD; 2µl tear sample will be collected using a glass capillary tube before application of any dyes to the ocular surface. Tears will be collected over a maximum period of 15 minutes.	Eurolens Research SOP # 57
7.20	LogMAR visual acuity	Distance high contrast visual acuity will be measured for each eye and binocularly. The acuity will be recorded to the nearest letter for each eye.	Eurolens Research SOP # 12a
7.21	Lens wear instructions	The subject will be instructed to wear the lenses for the rest of the day and not to remove the lenses before the next visit.	
7.22	End of Visit 7 and Instructions	Subject discharged and asked to return 14 ± 2 hours later (from the time of lens application).	

PART 2, VISIT 8

Subjects should attend Visit 8 wearing the study lenses which were applied at Visit 7 after 14 ± 2 hours. This is the final visit of Part 2.

Visit 8: Treatment 4 Follow-Up (after 14± 2 hours)			
Step	Procedure	Details	[redacted]
8.1	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
8.2	Compliance	Questions regarding the subject's contact lens wear since the previous visit. The number of hours of lens wear as well as the number of comfortable hours of lens wear will be recorded. N.B. Subjects should not have removed the lenses since the previous visit. If subjects have had to remove one or both lenses, the investigator should stop the visit at this point and a Final Evaluation form should be completed. All subjects are eligible to repeat Visits 7 and 8 of Part 2 on ONE more occasion on a different day if any problems with the lens wear occur between Part 2, Visits 7 and 8. If such problems do occur, Visit 7 will also need to be repeated.	
8.3	Subject Reported Ocular Symptoms	Record subject reported ocular symptoms.	
8.4	Subjective comfort	Subjective comfort scores for each lens (OD and OS) separately using a vertical VAS scale will be recorded.	[redacted]
8.5	LogMAR visual acuity & over-refraction	Distance high contrast visual acuity will be measured for each eye and binocularly as well as after an over-refraction.	Eurolens Research SOP # 12a
8.6	Lens fitting and surface assessment	Lens fit will be measured using a slit lamp graticule for the following:	Eurolens Research SOP # 24

Visit 8: Treatment 4 Follow-Up (after 14± 2 hours)			
Step	Procedure	Details	[redacted]
		Coverage: Nasal coverage Temporal Coverage Inferior Coverage Superior Coverage **Centration:** Horizontal centration (by auto calculation) Vertical centration (by auto calculation) **Movement** in primary position The lens surface will be recorded according to the following integer scales: lens deposits (0-2), deposit degree (0-4), lens debris (0-4) and lens wettability (0-4).	Eurolens Research Grading Scale (surface assessment)
8.7	Tear meniscus height	The OD lower tear meniscus will be imaged using the OCT. Three images will be taken.	Eurolens Research SOP # 58
8.8	Non-invasive tear break-up time	OD tear film break up time will be measured using the Medmont topographer Three measurements will be undertaken.	Eurolens Research SOP # 16
8.9	Tear film osmolarity	OD osmolarity measured using the Tearlab. Two measurements will be undertaken.	Eurolens Research SOP # 52
8.10	Tear sample collection	OD; 2µl tear sample will be collected using a glass capillary tube before application of any dyes to the ocular surface.	Eurolens Research SOP # 57

Visit 8: Treatment 4 Follow-Up (after 14± 2 hours)			
Step	Procedure	Details	[redacted]
		Tears will be collected over a maximum period of 15 minutes.	
8.11	Lens removal	Lenses will be removed and discarded.	
8.12	Subjective comfort	Subjective comfort scores using a vertical VAS scale will be recorded for each eye separately.	[redacted]
8.13	Ocular surface and lid margin staining photography and grading	OS: Sodium fluorescein will be added to the ocular surface and the following will be graded using Efron scales: corneal and bulbar conjunctival staining. OS ONLY: Lissamine green will then be added to the ocular surface and photographs of the upper and lower lid margin staining will be taken. These images will be used to subjectively grade lid margin staining at the time of the visit and for subsequent automated image analysis.	Eurolens Research SOP #13 Eurolens Research SOP #41

FINAL EVALUATION

The final evaluation will take place immediately following the last scheduled follow-up visit per the study protocol. It may also take place at any point the subject discontinues the study or is terminated from the study.

Final Evaluation			
Step	Procedure	Details	[redacted]
F.1	Final Exam Form	Indicate if the subject completed the study successfully. If subject discontinued from the study, indicate the reason.	
F.2	Exit slit lamp biomicroscopy	The Efron slit lamp classification scale will be used to grade the findings. Adverse events will be documented and followed for significant slit lamp findings.	Eurolens Research SOP # 13
F.3	Exit Visual Acuity	Record distance high contrast LogMAR visual acuity (OD, OS and OU) with their with their refractive correction from Part 1, Visit 1 (or habitual spectacles) in place.	Eurolens Research SOP # 12a

7.3. Unscheduled Visits

If, during the investigation, a subject requires an unscheduled visit to the clinical site, the following information will be collected at a minimum:

- Chief complaint prompting the visit. If the reason is an adverse event, the applicable eCRF for the adverse event must be completed and subject record completed as appropriate
- Date and time of the visit and all procedures completed at the unscheduled visit
- Review of adverse event and concomitant medications
- Documentation of any test article dispensed or collected from the subject, if applicable
- Slit lamp findings (using the Slit Lamp Classification Scale)

If the Investigator withdraws a subject from the study, the final study visit case report forms must be completed indicating the reason(s) why the subject was withdrawn. The subject record must be completed documenting the date and primary reason for withdrawal and the study CRA notified.

Any ocular and non-ocular Adverse Events that are ongoing at the time of the study visit will be followed by the Investigator, within licensure, until they have resolved, returned to pre-treatment status, stabilized, or been satisfactorily explained. If further treatment i.e., beyond licensure is required, the subject will be referred to the appropriate health care provider.

The following information will be collected during an unscheduled visit.

Unscheduled Visit			
Step	Procedure	Details	[redacted]
U.1	Chief Complaints	Record the subject's chief complaints for reasons for the unscheduled visit.	
U.2	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
U.3	LogMAR visual acuity	Distance high contrast visual acuity will be measured for each eye and binocularly (using spectacles, habitual lenses, study lenses, or unaided as appropriate)	Eurolens Research SOP # 12a
U.4	Subjective sphero-cylindrical refraction	Subjective sphero-cylindrical refraction will be performed on both eyes	
U.5	LogMAR visual acuity	Distance high contrast visual acuity will be measured OD,OS and OU with the subjective refraction in place.	Eurolens Research SOP # 12a
U.6	Slit lamp biomicroscopy	The Efron slit lamp classification scale will be used to grade the findings in accordance with the current Eurolens Research Standard	Eurolens Research SOP # 13

Unscheduled Visit			
Step	Procedure	Details	[redacted]
		Operating Procedures 'Examination of the Anterior Segment Using Slit Lamp Biomicroscopy'. Grades will be scored to the nearest 0.1 in the best judgment of the investigator using Efron Grading Scales.	
U.7	Lens dispensing	Dispense study lenses. The same dispensing criteria and instructions should be followed as at previous visits	
U.8	Exit Visual Acuity	Distance high contrast visual acuity (OD, OS, OU) will be measured with the subject's habitual spectacle correction in place or unaided if appropriate.	Eurolens Research SOP # 12a

7.4. Laboratory Procedures

Study lenses and tear samples will be frozen for subsequent laboratory analysis. Samples will initially be stored at -20 °C but will be transferred (using dry ice) to a -80°C freezer within three working days.

8. SUBJECTS COMPLETION/WITHDRAWAL

8.1. Completion Criteria

Subjects are considered to have completed the study if they:

- provided informed consent
- they are eligible
- completed all visits through the final visit (Part 2, Visit 8)

8.2. Withdrawal/Discontinuation from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Subject death during the study period
- Subject withdrawal of consent
- Subject not compliant to protocol including use of non-study lenses or not reaching the required wear times
- Subject lost to follow-up
- Subject no longer meets eligibility criteria (e.g. the subject becomes pregnant)
- Subject develops significant or serious adverse events causing discontinuation of study lens wear (more than 7 days)
- Subjects who have experienced a Corneal Infiltrative Event (CIE)
- Investigator's clinical judgment regarding the subject safety reasons (that it is in the best interest of the subject to stop treatment)
- Subject missed a study visit

- Subject not compliant with study lens wear schedule
- Subject not successfully dispensed due to lack of efficacy and safety including poor vision, poor comfort or unacceptable fit

For discontinued subjects, the Investigator will:

- Complete the current visit (scheduled or unscheduled)
- Complete the Final Evaluation, indicating the reason that the subject was discontinued from the study
- Record the spherocylindrical refraction with best corrected distance visual acuity
- Collect used test article(s) (worn or brought to the visit) from the subject and discard them, unless otherwise stated in section 7.2.
- Collect all unused test article(s) from the subject

An additional subject will be enrolled if a subject discontinues from the study prematurely.

In cases where a subject is lost to follow-up, every possible effort must be made to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented including two written attempts and a certified letter (or equivalent) as the final attempt.

9. PRE-STUDY AND CONCOMITANT INTERVENTION/MEDICATION

Concomitant medications will be documented during screening and updated during the study. Disallowed medications for this study include: any ocular topical medications (including comfort drops) and any systemic medications that in the view of the investigator may affect the ocular surface or contact lens wear from 24 hours prior to study visits.

Concomitant therapies that are disallowed include: any that the investigator feels may significantly affect contact lens wear.

10. DEVIATIONS FROM THE PROTOCOL

Investigator will notify study sponsor upon identification of a protocol deviation. Major protocol deviations must be reported to the sponsor within 24 hours after discovery of the protocol deviation. The Investigator will report deviations per IRB/IEC requirements. All deviations will be tracked and corrective actions implemented as appropriate.

If it becomes necessary for the Investigator to implement a deviation in order to eliminate an immediate hazard to the trial subject, the Investigator may implement the deviation immediately without notification to the sponsor. Within 24 hours after the implemented deviation, the Investigator must notify and provide the rationale to the Sponsor and, as required, the IEC/IRB.

11. STUDY TERMINATION

The occurrence of one or more Unanticipated Serious Adverse Device Effect (USADE), or any SAE where the relationship to study agent cannot be ruled out, may result in stopping further dispensing of test article. In the event of a USADE or SAE, the Sponsor may unmask the treatment regimen for the subject(s) and will discuss this with the Investigator before any further subjects are enrolled.

The Sponsor will determine when a study will be stopped. The Principal Investigator always has the discretion to initiate stopping the study based on patient safety or if information indicates the study's results are compromised.

JJVC reserves the right to terminate the study at any time for any reason. Additionally, the IEC/IRB reserves the right to terminate the study if an unreasonable risk is determined. The study can be terminated by the Principal Investigator at the individual clinical site due to specific clinical observations, if in their opinion, after a discussion with JJVC, it is determined that it would be unwise to continue at the clinical site.

JJVC (and the IEC/IRB and DMC, if applicable) will evaluate all adverse events. If it is determined that an adverse event presents an unreasonable risk, the investigation, or that part of the investigation presenting the risk, will be terminated, as soon as possible.

Should the study be terminated (either prematurely or as scheduled), the Investigator will notify the IEC/IRB and Regulatory Authority as required by local regulatory requirements.

12. PROCEDURE FOR HANDLING PRODUCT QUALITY COMPLAINTS

A Product Quality Complaint (PQC) refers to any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of test articles after they have been released for clinical trial use.

Potential complaints may come from a variety of sources including but not limited to subjects, clinical research associates (CRA), clinical operations managers (COM), medical monitors, and site personnel, etc. The following are not considered product quality complaints:

- Subject satisfaction inquiries reported via "Subjective Questionnaires" and "Patient Reported Outcomes (PRO)"
- Clinical test articles that are stored improperly or damaged after receipt at the investigational site
- Lens replacements that occur due to drops/fall-outs
- Damage deemed by clinicians or clinical staff to be caused by handling by the user, and not indicative of a quality deficiency (i.e. tears, rips, etc.), only in situations where there is no deficiency alleged by the subject

Within 24 hours of site personnel becoming aware that a PQC has occurred, the PQC must be recorded in the EDC system, which will trigger an automatic email notification to the appropriate COM/CRA and Clinical QA representative. In cases where the EDC system in use

is not configured to send automatic notifications or when an EDC system is not used, the COM/CRA is responsible for notifying Clinical QA upon discovery that a PQC has occurred.

Upon receipt of the EDC notification, the COM/CRA will contact the study site to collect additional information which will include:

- Date the complaint was received/recorded in the EDC System (Date of Sponsor Awareness)
- Who received the complaint
- Study number
- Clinical site information (contact name, site ID, telephone number)
- Lot number(s)
- Unique Subject Identifier(s)
- Indication of who first observed complaint (site personnel or subject)
- OD/OS indication, along with whether the lens was inserted
- Any related AE number if applicable
- Detailed complaint description (scheduled/unscheduled visit, wear time, symptoms, resolution of symptoms, etc.)
- Eye Care Provider objective (slit lamp) findings if applicable
- Confirmation of product availability for return (and tracking information, if available), or rationale if product is not available for return (Refer to Form Control No. [redacted] for test article return instructions)

Once a complaint is received, it will be assessed by the COM, CRA, or trained site personnel to determine if it is an Adverse Event/Serious Adverse Event (AE/SAE). If the complaint results in an AE/SAE, the COM/CRA, or trained site personnel will follow Section 13 of this protocol. If the AE/SAE was potentially the result of a product quality related deficiency, these procedures also applies and will be executed in parallel.

In some cases, a PQC form may be generated in EDC by the site in error. In this event, the PQC forms will be marked “Intentionally Left Blank” or “ILB”. Justification for ILB must be documented.

13. ADVERSE EVENTS

13.1. Definitions and Classifications

Adverse Event (AE) – 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.
Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.
Note 2 to entry: This definition includes events related to the procedures involved.
Note 3 to entry: For users or other persons, this definition is restricted to events related to investigational medical devices.”[1]

An AE includes any condition (including a pre-existing condition) that:

1. Was not present prior to the study, but appeared or reappeared following initiation of the study
2. Was present prior to the study, but worsened during the study. This would include any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of disease states
3. Pregnancy must be documented as an adverse event and must be reported to the clinical monitor and to the Sponsor immediately upon learning of the event

Serious Adverse Event (SAE) – An SAE is any untoward medical occurrence that:

- Results in death
- Is life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (e.g., a sight threatening event, a significant persistent or permanent change, impairment, damage, or disruption to the subject's body)
- Is a congenital anomaly/birth defect, or
- Requires intervention to prevent permanent damage (the use of the test article resulting in a condition which requires medical or surgical intervention to preclude permanent impairment of the body structure or a body function). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Diagnoses and conditions that are considered Ocular Serious Adverse Events include, but not limited to:

- Microbial Keratitis (MK)
- Iritis (including cells in the anterior chamber)
- Permanent decrease in best spectacle corrected visual acuity equivalent to 2 acuity lines or greater
- Central Corneal Opacity
- Central Corneal Neovascularization
- Uveitis
- Endophthalmitis
- Hypopyon
- Hyphemia
- Penetration of Bowman's Membrane
- Persistent Epithelial Defect
- Limbal cell Damage leading to Conjunctivalization

Significant Adverse Events – Those events that are usually symptomatic and warrant discontinuation (temporary or permanent) of the test article (excluding Serious Adverse Events).

Diagnoses and conditions that are considered Ocular Significant Adverse Events include, but not limited to the following:

- Contact Lens Induced Peripheral Ulcer (CLPU)
- Significant Infiltrative Events (SIE)
- Superior Epithelial Arcuate Lesions (SEALs)
- Any Temporary Loss of > 2 Lines of BSCVA
- Other grade 3 or higher corneal findings, such as abrasions or edema
- Non-contact lens related corneal events - e.g. Epidemic Keratoconjunctivitis (EKC)
- Asymptomatic Corneal Scar
- Any corneal event which necessitates temporary lens discontinuation > 2 weeks

Non-Significant Adverse Events – Those conditions that are usually asymptomatic and usually do not warrant discontinuation (temporary or permanent) of the test article. However, the Investigator may choose to treat as a precautionary measure.

Diagnoses and conditions that are considered Ocular Non-Significant Adverse Events include, but not limited to the following:

- Non-significant Infiltrative Event (NSIE)
- Contact Lens Papillary Conjunctivitis (CLPC)
- Superficial Punctate Keratitis (SPK)
- Conjunctivitis: Bacterial, Viral, Allergic
- Blepharitis
- Meibomianitis
- Contact Dermatitis
- Localized Allergic Reactions
- Any corneal event not explicitly defined as serious or significant adverse event, which necessitates temporary lens discontinuation < 2 weeks

Adverse Device Effect (ADE) – An ADE is an "adverse event related to the use of an investigational medical device.
Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device."[1]

Unanticipated Adverse Device Effect (UADE) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the test article, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, Investigator's Brochure or protocol, or any other unanticipated serious problem associated with the test article that relates to the rights, safety and welfare of subjects.

13.2. Assessing Adverse Events

In conjunction with the medical monitor, the Investigator will evaluate adverse events to ensure the events are categorized correctly. Elements of categorization will include:

- Seriousness/Classifications (see definition in Section 13.1)
- Causality or Relatedness – i.e. the relationship between the test article, study treatment or study procedures and the adverse event (not related; unlikely related; possibly related; related - see definition in Section 13.2.1)
- Adverse Event Severity – Adverse event severity is used to assess the degree of intensity of the adverse event (mild; moderate; severe for all events - see definition in Section 13.2.2)
- Outcome – not recovered or not resolved; recovering or resolving; recovered or resolved with sequelae; recovered or resolved; death related to adverse event; unknown
- Actions Taken – none; temporarily discontinued; permanently discontinued; other

13.2.1. Causality Assessment

Causality Assessment – A determination of the relationship between an adverse event and the test article. The test article relationship for each adverse event should be determined by the investigator using these explanations:

- Not Related- An adverse event that is not related to the use of the test article, study treatment or study procedures
- Unlikely Related – An adverse event for which an alternative explanation is more likely, e.g. concomitant treatment, concomitant disease(s), or the relationship of time suggests that a causal relationship is not likely
- Possibly Related – An adverse event that might be due to the use of the test article, or to the study treatment or study procedures. An alternative explanation, e.g. concomitant treatment, concomitant disease(s), is inconclusive. The relationship in time is reasonable. Therefore, the causal relationship cannot be excluded
- Related – An adverse event that is listed as a possible adverse effect (device) or adverse reaction (drug) and cannot be reasonably explained by an alternative explanation, e.g. concomitant treatment of concomitant disease(s). The relationship in time is very suggestive, e.g. it is confirmed by de-challenge and re-challenge

13.2.2. Severity Assessment

Severity Assessment – A qualitative assessment of the degree of intensity of an adverse event as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article, study treatment or study procedure relationship or seriousness of the event and should be evaluated according to the following scale:

- Mild – Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities
- Moderate – Event is bothersome, possible requiring additional therapy, and may interfere with the subject's daily activities
- Severe – Event is intolerable, necessitates additional therapy or alteration of therapy and interferes with the subject's daily activities

13.3. Documentation and Follow-Up of Adverse Events

The recording and documenting of adverse events (ocular and non-ocular) begins when the subjects are exposed to the test article, study treatment or study procedure. Adverse events reported before the use of test article, start of study treatment, or study procedures will be recorded as medical history. However, if the condition deteriorates at any time during the study it will be recorded and reported as an AE. Untoward medical events reported after the subject's exit from the study will be recorded as adverse events at the discretion of the Investigator.

Upon finding an adverse event, the Principal Investigator will document the condition in the subject record and in the eCRFs. He/she will complete the Adverse Event /eCRF.

Complete descriptions of all adverse events must be available in the subject record. All Adverse Events including local and systemic reactions not meeting the criteria for "serious adverse events" shall be captured on the appropriate case report form or electronic data system. All adverse events occurring while the subject is enrolled in the study must be documented appropriately regardless of relationship.

It is the Investigator's responsibility to maintain documentation of each reported adverse event. All adverse events will be followed in accordance with applicable licensing requirements. Such documentation will include the following:

- Adverse event (diagnosis not symptom)
- Drawings or photographs (where appropriate) that detail the finding (e.g., size, location, and depth, etc.)
- Date the clinical site was notified
- Date and time of onset
- Date and time of resolution
- Adverse event classification, severity, and relationship to test articles, as applicable
- Treatment regimen instituted, including concomitant medications prescribed, in accordance with applicable licensing requirements
- Any referral to another health care provider if needed
- Outcome, ocular damage (if any)
- Likely etiology
- Best corrected visual acuity at the discovery of the event and upon conclusion of the event

In addition, if an infiltrate(s) is present, he/she will complete the Corneal Infiltrate Assessment eCRF. Where necessary, a culture of the corneal lesion will be collected to determine if the infection is microbial in nature. If cultures are collected, the date of culture collection and laboratory utilized will be recorded.

Changes in the severity of an AE shall be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of the onset and duration of each episode. Changes in the assessment of relationship to the Test Article shall also be clearly documented.

Subjects who present with an adverse event shall be followed by the Investigator, within licensure, until all signs and symptoms have returned to pre-treatment status, stabilized, or been satisfactorily resolved. If further treatment beyond licensure is required, the patient will be referred to the appropriate health care provider. The Investigator will use his/her clinical judgment as to whether a subject reporting with an adverse event will continue in the study. If a subject is discontinued from the study, it will be the responsibility of the Investigator to record the reason for discontinuation. The Investigator will also document the adverse event appropriately and complete the Adverse Event eCRF. Any subjects with ongoing adverse events related to the test article, study treatment or study procedures, as of the final study visit date, should be followed to resolution of the adverse event or until referral to an appropriate health care provider, as recommended by the Investigator. Non-ocular adverse events that are not related to the test article, study treatment, or study procedures may be recorded as "ongoing" without further follow-up.

13.4. Reporting Adverse Events

The Investigator will notify the Sponsor of an adverse event by e-mail, facsimile, or telephone as soon as possible and no later than 24 hours from discovery for any serious /significant adverse events, and 2 days from discovery for any non-significant adverse event. In addition, a written report will be submitted by the Principal Investigator to the IEC/IRB according to their requirements (Section 13.4.2). The report will comment whether the adverse event was considered to be related to the test article, study treatment or study procedures.

13.4.1. Reporting Adverse Events to Sponsor

Serious/Significant Adverse Events

The Investigator will inform the sponsor of all serious/significant adverse events occurring during the study period as soon as possible by e-mail, fax, or telephone, but no later than 24 hours following discovery of the event. The Investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the eCRF. All subjects experiencing a serious/significant adverse event must be followed up and all outcomes must be reported.

When medically necessary, the Investigator may break the randomization code to determine the identity of the treatment that the subject received. The Sponsor and study monitor should be notified prior to unmasking the test articles.

In the event of a serious/significant adverse event, the Investigator must:

- Notify the Sponsor immediately
- Obtain and maintain in the subject's records all pertinent medical information and medical judgment for colleagues who assisted in the treatment and follow-up of the subject
- Provide the Sponsor with a complete case history which includes a statement as to whether the event was or was not related to the use of the test article
- Notify the IEC/IRB as required by the IEC/IRB reporting procedure according to national regulations

Unanticipated (Serious) Adverse Device Effect (UADE)
In the event of an Unanticipated (Serious) Adverse Device Effect (UADE), the Investigator will submit a report of the UADE to the Sponsor and IEC/IRB as soon as possible, but no later than 24 hours after the Investigator first learns of the effect. This report is in addition to the immediate notification mentioned above.

The Sponsor must conduct an evaluation of the UADE and must report the results of the evaluation to FDA, the IEC/IRB and participating Investigators within 10 working days after the Sponsor first receives notification of the effect.

Non-Serious Adverse Events
All non-serious adverse events, including non-serious adverse device effects, will be reported to the sponsor by the Investigator no later than 2 days from discovery.

13.4.2. Reporting Adverse Events to the Responsible IEC/IRB and Health Authorities

Adverse events that meet the IEC/IRB requirements for reporting must be reported within the IEC/IRB's written guidelines. Each clinical site will refer to and follow any guidelines set forth by their Approving IEC/IRB. Each clinical site will refer to and follow any guidelines set forth by their local governing Health Authorities.

The Sponsor will report applicable Adverse Events to the local health authorities according the written guidelines, including reporting timelines.

13.4.3. Event of Special Interest

None

13.5. Reporting of Pregnancy

Subjects reporting pregnancy (by self-report) during the study will be discontinued after the event is recorded as an Adverse Event. Once discontinued, pregnant participants and their fetuses will not be monitored for study related purposes. Pregnant participants are not discontinued from contact lens or solution related studies for safety concerns, but due to general concerns relating to pregnancy and contact lens use. Specifically, pregnant women are discontinued due to fluctuations in refractive error and/or visual acuity that occur secondary to systemic hormonal changes, and not due to unforeseen health risks to the mother or fetus.

14. STATISTICAL METHODS

14.1. General Considerations

Statistical Analysis will be undertaken by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be implemented in this clinical trial is outlined below. More details will be included in the stand-alone Statistical Analysis Plan (SAP). The SAP will be developed and finalized prior to database lock.

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 or higher (SAS Institute, Cary, NC). Throughout the analysis of data, the results for each subject/eye will be used when available for summarization and statistical analysis. Unscheduled visits will be summarized separately and will be excluded from the statistical analysis.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables and safety variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

14.2. Sample Size Justification

The sample size was not determined by any empirical power calculation. The plan is to enroll approximately 210-240 subjects with a completion target of 27 subjects per strata (Symptomatic and Asymptomatic). Assuming a sample of size 27 subjects per strata, the statistical power was calculated using SAS procedure PROC POWER. The goal is to show Symptomatic subjects have, on average, lower Non-invasive tear Breaks up Time (NIBUT) and Tear Meniscus Height (TMH); and greater Lid Margin Staining (LMS), Tear Film Osmolarity (OSM), and White Blood Cell (WBC) count compared to Asymptomatic subjects.

Table 4 contains the information of two previous studies and their corresponding subject disposition. Tables 5 to Table 9 below summarizes the primary endpoints from the studies [redacted] and [redacted] that are corresponded to the current study and therefore used to compute the power.

Table 4: Historical Studies Included

Study	Study Design	Endpoints Collected	No. of Enrolled	No. of Completed - Asymptomatic	No. of Completed - Symptomatic
[redacted]	Cross-sectional study of subjects wearing Dailies AquaComfort Plus	Lid Margin Staining, NIBUT, TMH, Tear film osmolarity,	42	25	16
[redacted]	Cross-sectional study of subjects	Lid Margin Staining,	74	27	15

	wearing their habitual lenses	White blood Cell Count			

Table 5: Lid Margin Staining – Completed Per-Protocol Population [redacted]

LMS (Mean [STD]) **	**Eyelid**	**Strata**	
		Asymptomatic N=50	**Symptomatic N=32**
Baseline	Lower	0.98 (0.95)	1.15 (0.75)
	Upper	0.79 (0.75)	0.68 (0.58)
14-Hours Post Lens Insertion	Lower	1.34 (0.77)	1.47 (0.72)
	Upper	0.74 (0.89)	1.31 (0.87)

N=Number of eyes.

Table 6: Non-Invasive Tear Break-Up Time (NITBUT in Seconds) – Completed Per-Protocol Population [redacted]

NIBUT (Mean [STD]) **	**Strata**	
	Asymptomatic N=25	**Symptomatic N=16**
Post Lens Insertion	13.19 (8.917)	11.47 (7.035)
14-Hours Post Lens Insertion	9.46 (4.608)	8.34 (4.660)

N=Number of Subjects
**Averaged across three measurements

Table 7: Tear Meniscus Height (TMH) – Completed Per-Protocol Population [redacted]

TMH (Mean [STD]) **	**Eyelid**	**Strata**	
		Asymptomatic N=50	**Symptomatic N=16**
Baseline	Lower	0.21 (0.054)	0.21 (0.059)
	Upper	0.16 (0.036)	0.017 (0.034)
Post Lens Insertion	Lower	0.20 (0.056)	0.19 (0.048)
	Upper	0.16 (0.041)	0.15 (0.036)
14-Hours Post Lens Insertion	Lower	0.18 (0.065)	0.14 (0.067)
	Upper	0.14 (0.044)	0.12 (0.030)

N=Number of eyes.
**Averaged across three measurements

Table 8: Tear Film Osmolarity (mOsm/L) – Completed Per-Protocol Population [redacted]

TOSM (Mean [STD]) **	**Strata**	
	Asymptomatic N=25	**Symptomatic N=16**
Post Lens Insertion	319.52 (75.538)	297.47 (10.899)
14-Hours Post Lens Insertion	301.38 (34.473)	288.41 (58.943)

N=Number of Subjects
**Averaged across two measurements

Table 9: Mean White Bloods Cell (WBC) Count (Confocal Microscopy) – Completed Per-Protocol Population [redacted]

Mean[STD]	Eyelid	Strata/Eye			
		Asymptomatic N=27		Symptomatic N=15	
		Left	Right	Left	Right
Visit 2 (2-14 Days after Visit 1)	Lower	3.044 (2.7755)	4.062 (4.8873)	6.175 (5.8041)	6.533 (4.1495)
	Upper	3.006 (3.1092)	4.130 (3.9155)	6.277 (6.8528)	5.633 (5.5359)
Visit 3 (2-14 Days after Visit 2)	Lower	2.957 (2.8150)	3.790 (4.7627)	4.444 (4.7879)	6.555 (6.6327)
	Upper	3.197 (3.8542)	4.253 (4.0071)	8.267 (10.5946)	9.301 (10.8690)

N=Number of Subjects [redacted]

The power calculation of LMS, NIBUT, TMH, and TOSM were conducted for the combination of the different effect sizes (Δ = Symptomatic – Asymptomatic) and the different common variances (σ). The power calculation of WBC was conducted for the combination of the different mean ratios (ϕ =Symptomatic/Asymptomatic) and the different common coefficient of variances (CV). CV, also known as the relative standard deviation, is the ratio of the standard deviation to the mean.

The parameters $\Delta, \sigma, \phi,$ and CV were estimated from the data of [redacted] and [redacted]. Historical data suggest that increasing the effect sizes or the mean ratios and decreasing the standard deviation or the coefficient of variations increases the power. For the fixed number of 27 subjects per strata, the criteria that need to be satisfied in order to obtain ~80% power corresponding to the primary hypotheses are presented below in Table 10 to Table 14:

1. Hypothesis 1: Symptomatic subjects will have, on average, greater upper and lower lid margin staining (LMS) compared to asymptomatic subjects after 14 hours of lens wear.

Table 10: Power Calculations of LMS for N=54

	Common standard deviation (σ)		
Effect size (Δ)	0.5	0.7	0.9
0.30	70%	46%	33%
0.35	81%	57%	41%
0.40	90%	67%	49%

The sample size is sufficiently large to demonstrate greater LMS with ~80% power to Symptomatic subjects if $\Delta \geq 0.35$ and $\sigma \leq 0.5$.

2. Hypothesis 2: Symptomatic subjects will have, on average, shorter NIBUT compared to asymptomatic subjects after 14 hours of lens wear.

Table 11: Power Calculations of NIBUT for N=54

	Common standard deviation (σ)		
Effect size (Δ)	3	4	5
-2.1	81%	60%	45%
-1.1	38%	26%	20%
0.0	5%	5%	5%

The sample size is sufficiently large to demonstrate lower NIBUT with ~80% power to Symptomatic subjects if $\Delta \leq -2.1$ and $\sigma \leq 3$.

3. Hypothesis 3: Symptomatic subjects will have, on average, lower TMH compared to asymptomatic subjects after 14 hours of lens wear.

Table 12: Power Calculations of TMH for N=54

	Common standard deviation (σ)		
Effect size (Δ)	0.04	0.06	0.08
-0.04	98%	78%	56%
-0.03	86%	57%	39%
-0.01	23%	15%	12%

The sample size is sufficiently large to demonstrate lower TMH with ~80% power to Symptomatic subjects if $\Delta \leq -0.03$ and $\sigma < 0.06$.

4. Hypothesis 4: Symptomatic subjects will have, on average, greater tear film osmolarity (TOSM) compared to asymptomatic subjects after 14 hours of lens wear.

Table 13: Power Calculations of TOSM for N=54

	Common standard deviation (σ)		
Effect size (Δ)	20	25	30
10	57%	42%	33%
12	70%	54%	42%
14	81%	65%	52%

The sample size is sufficiently large to demonstrate greater TOSM with ~80% power to Symptomatic subjects if $\Delta \geq 14$ and $\sigma \leq 20$.

5. Hypothesis 5: Symptomatic subjects will have, on average, greater mean number of white blood cells (WBC) (visualized by confocal microscopy) in both the upper and lower lid margins compared to asymptomatic subjects after 6 hours of lens wear.

Table 14: Power Calculations of WBC for N=54

	Common coefficient of variances (CV)		
Mean ratio (ϕ)	0.65	1.0	1.3
1.0	5%	5%	5%

1.5	80%	55%	43%
2.0	100%	92%	81%

The sample size is sufficiently large to demonstrate greater WBC with ~80% power to Symptomatic subjects if $\phi \geq 1.5$ and $CV \leq 0.65$; and $\phi \geq 2$ and $CV \leq 1.3$.

14.3. Analysis Populations

Safety Population:
All subjects who were administered any test article excluding subjects who drop out prior to administering any test article. At least one observation should be recorded.

Per-Protocol Population:
All subjects who have successfully completed all visits and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database hard lock (Per-Protocol Population). Justification of excluding subjects with protocol deviations in the per-protocol population set will be documented in a memo to file.

Intent-to-Treat (ITT) Population:
All randomized subjects regardless of actual treatment and subsequent withdrawal from study or deviation from protocol. At least one observation should be recorded.

14.4. Level of Statistical Significance

Each pre-planned primary and secondary hypothesis will be analyzed with a two-sided type I error rate of 5%.

14.5. Primary Analysis (For Part 1)

Lid Margin Staining (LMS)
Model-1: Upper and lower eyelids' average LMS (average of Horizontal and sagittal grades) after 14-hours follow-up will be analyzed using a linear mixed model by adjusting the baseline LMS as a covariate.
Model-2: Final eyelid's average (average of the upper and lower lid average) LMS after 14-hours follow-up will be analyzed using a linear model by adjusting the baseline LMS as a covariate.
Both the models will include subject strata (asymptomatic/symptomatic) as fixed effect, however, only model-1 will include subject as random effect (G-side). Other characteristics such as age, gender, and race will be included as fixed covariates when appropriate. For only model-1, different covariance structures will be considered to model the residual errors between the lower and upper eyelids' average LMS from the same subject (R-side). The covariance structure will be selected based on the finite-sample corrected Akaike's Information Criterion[10]. The following covariate structures will be considered:

- Unstructured Covariance Structure (UN)
- Homogenous Compound symmetry (CS)

Comparisons between subject strata for LMS will be carried out using a one-sided 95% CI of least-square means differences (symptomatic - asymptomatic) at 14-hour follow-up for the hypothesis given below:

$$H_0: \mu_S - \mu_A \leq 0$$
$$H_A: \mu_S - \mu_A > 0,$$

where S=Symptomatic and A=Asymptomatic. For only model-1, adjustments for multiple comparisons across lower and upper eyelids' will be performed using a simulation method with alpha equal to 0.05 (Edwards and Berry, 1987)[13].A statistically greater upper and lower LMS, on average, for symptomatic subjects compared to asymptomatic subjects after 14 hours of lens wear will be concluded if the lower limit of the 95% confidence intervals for the least-squares means is greater than 0.

Non-invasive tear break-up time (NIBUT) and Tear Meniscus Height (TMH)

NIBUT and TMH will be analyzed using a linear mixed model separately by adjusting the baseline as a covariate. The model will include subject strata (asymptomatic/symptomatic), time event (i.e., fitting and 14-hours follow-up), and strata by time event interaction as fixed effects; subject will be included as random effects (G-side). Other characteristics such as age, gender, and race will be included as fixed covariates when appropriate. Different covariance structures will be considered to model the residual errors between the repeated measurements within time event from the same subject (R-side). The covariance structure will be selected based on the finite-sample corrected Akaike's Information Criterion[10]. The following covariate structures will be considered:

- Unstructured Covariance Structure (UN)
- Homogenous Compound symmetry (CS)
- Heterogeneous Compound Symmetry (CSH)
- Spatial Power (SP[POW])

For SP(POW) covariance structure, subject and time event within subject will be included as random effects. For the remaining structures, only subject will be included as a random effect. The structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fit the data. Heterogeneous covariance structures across strata may be considered if necessary. The Kenward and Roger method (Kenward and Roger, 1997)[11] will be used for the denominator degree of freedom.

Comparisons between subject strata for NIBUT and TMH will be carried out using a one-sided 95% CI of least-square means differences (symptomatic - asymptomatic) at 14-hour follow-up for the hypothesis given below:

$$H_0: \mu_S - \mu_A \geq 0$$
$$H_A: \mu_S - \mu_A < 0.$$

where S=Symptomatic and A=Asymptomatic. No multiple adjustment will be necessary since the hypothesis test will be conducted based on only 14-hour follow-up. A statistically shorter

NIBUT or lower TMH, on average, for symptomatic subjects compared to asymptomatic subjects after 14 hours of lens wear will be concluded if the upper limit of the 95% confidence intervals for the Least-squares means is less than 0.

Tear Film Osmolarity (TOSM)

TOSM will be analyzed using a linear mixed model by adjusting the baseline TOSM as a covariate. The model will include subject strata (asymptomatic/symptomatic), time event (i.e., fitting and 14-hours follow-up), and strata by time event interaction as fixed effects; subject will be included as random effects (G-side). Other characteristics such as age, gender, and race will be included as fixed covariates when appropriate. Different covariance structures will be considered to model the residual errors between the repeated measurements within time event from the same subject (R-side). The covariance structure will be selected based on the finite-sample corrected Akaike's Information Criterion[10]. The following covariate structures will be considered:

- Unstructured Covariance Structure (UN)
- Homogenous Compound symmetry (CS)

The structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fit the data. Heterogeneous covariance structures across strata may be considered if necessary. The Kenward and Roger method (Kenward and Roger, 1997)[11] will be used for the denominator degree of freedom.
Comparisons between subject groups for TOSM will be carried out using a one-sided 95% CI of least-square means differences (symptomatic - asymptomatic) at 14-hour follow-up for the hypothesis given below:

$$H_0: \mu_S - \mu_A \leq 0$$
$$H_A: \mu_S - \mu_A > 0,$$

where S=Symptomatic and A=Asymptomatic. No multiple adjustment will be necessary since the hypothesis test will be conducted based on only 14-hour follow-up. A statistically greater TOSM, on average, for symptomatic subjects compared to asymptomatic subjects after 14 hours of lens wear will be concluded if the lower limit of the 95% confidence intervals for the Least-squares means is greater than 0.

Number of White Blood Cells (WBC)

The number of white blood cells (visualized by confocal microscopy) after 6-hour follow up will be analyzed using a generalized linear mixed model with Poisson distribution and log link function. The model will include subject strata (asymptomatic/symptomatic) as fixed effects; subject will be included as random effects (G-side). Other characteristics such as age, gender, and race will be included as fixed covariates when appropriate. Different covariance structures will be considered to model the residual errors between the lower and upper lid margin measurements within eye from the same subject (R-side). The covariance structure will be selected based on the finite-sample corrected Akaike's Information Criterion[10]. The following covariate structures will be considered:

- Unstructured Covariance Structure (UN)
- Homogenous Compound symmetry (CS)

The structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fit the data. Heterogeneous covariance structures across strata may be considered if necessary. The Kenward and Roger method (Kenward and Roger, 1997)[11] will be used for the denominator degree of freedom.

The Comparison between the symptomatic and the asymptomatic strata will be carried out using one-sided 95% confidence intervals for the Least-squares means risk ratio (symptomatic over asymptomatic) at 6-hour follow up for the hypothesis given below:

$$H_0: \mu_S/\mu_A \leq 1$$
$$H_A: \mu_S/\mu_A > 1,$$

where S=Symptomatic and A=Asymptomatic. Adjustments for multiple comparisons across lower and upper lid margins will be performed using a simulation method with alpha equal to 0.05 (Edwards and Berry, 1987)[13]. A statistically significantly greater density of WBC, on average, in both the upper and lower lid margins for symptomatic subjects compared to asymptomatic subjects after 6 hours of lens wear will be concluded if the multiple adjusted lower limit of the 95% confidence intervals for the Least-squares means risk ratio is above 1.0.

Remark: For all the above models, the Kenward and Roger method implemented with the *kr2* option[12] in SAS will be used for the calculation of the denominator degrees of freedom. Heterogenous models across subject strata may be considered. The log-likelihood ratio test will be used to test for homogeneity between the two strata. Convergence limitations will be taken into account as necessary. If convergence is problematic, then reduced versions of the corresponding model will be considered. When the normality assumption does not hold for an endpoint, the analysis will be conducted on transformed data; generalized linear models or generalized linear mixed models with appropriate distributions will also be considered on the original data.

14.6. Secondary Analysis (For Part 1 and Part 2)

Relationship between Comfort Scores and Clinical Measures

Correlation analysis will be conducted between subjective comfort scores (VAS scale) and primary endpoints. Pearson product-moment correlation coefficient will be provided for continuous endpoints and Kendall's tau coefficient will be provided for ordinal endpoints. For each of the primary endpoints, when there is more than one measurement taken for each subject (eye for WBC), the mean will be used in the analysis and a test based on the corresponding correlation coefficient will be conducted separately.

Tests for the relationship between the comfort scores and each of the primary endpoints will be conducted separately using two-sided 95% confidence intervals constructed for the corresponding correlation coefficient. The relationship between comfort scores and a primary

endpoint will be concluded to be significant if 0 does not fall within confidence limits of the corresponding coefficient. The directional statistical relationship will be determined using the upper or lower limit of the 95% confidence interval. Upper limit below zero or lower limit above zero of the 95% confidence will determine negative or positive relationship, respectively, between the clinical measure and the VAS score. Further analysis based on a linear model or a generalized linear model depending on the distribution of the VAS scale may be undertaken if necessary when the relationship between comfort scores and any one of primary endpoints is significant.

14.7. Other Hypotheses

For Part 2:
The analysis procedure will follow the exact steps for analyzing these hypotheses as described in the primary analysis section for LMS, NIBUT, TMH, TOSM, and WBC.

For Part 1 and 2:

1. For Part 1 and 2: End of day discomfort will return to pre-lens wear comfort levels following lens removal.

Within each stratum and overall post VAS score for both eyes will be analyzed separately using a linear mixed model by adjusting the baseline VAS score (pre-VAS) as covariate. The model will include subject strata (asymptomatic/symptomatic) as fixed effect. Other characteristics such as, age, gender, and race will be included as fixed covariates when appropriate. Unstructured (UN) and Homogenous Compound symmetry (CS) Covariances will be considered to model the residual errors between the eyes from the same subject (R-side). A two-sided 95% CI for the coefficient of the model intercept will be constructed for the hypothesis given below:

$$H_0: \beta_{int} = 0$$
$$H_A: \beta_{int} \neq 0,$$

where β_{int} =model intercept. End of day discomfort returned to pre-lens wear comfort will be concluded if the 95% confidence intervals contains 0. Otherwise, statistical difference between end of day comfort and pre-lens comfort will be concluded. The direction will be determined using the upper or lower limit of the 95% confidence interval. Upper limit below zero or lower limit above zero of the 95% confidence will determine negative or positive change, in other words, lower or higher post VAS score compared to pre-VAS score, respectively.

2. There will be a relationship between change in CLDEQ score between Part 1 and Part 2 and change in the five clinical parameters investigated between Part 1 and Part 2.

Correlation analysis will be conducted for the change in CLDEQ score and the change in the five clinical parameters between Part 1 and Part 2. Pearson product-moment correlation coefficient will be provided for continuous endpoints, and Kendall's tau coefficient will be

provided for ordinal endpoints. For each of the primary endpoints, when there is more than one measurement taken for each subject (eye for WBC), the mean will be used in the analysis and a test based on the corresponding correlation coefficient will be conducted for each of the endpoints separately using two-sided 95% confidence intervals. The relationship of the endpoints will be concluded to be significant if 0 does not fall within confidence limits of the corresponding coefficient. The directional statistical relationship will be determined using the upper or lower limit of the 95% confidence interval. Upper limit below zero or lower limit above zero of the 95% confidence will determine negative or positive relationship, respectively, between the clinical measures.

3. There will be a relationship between change in CLDEQ score between Part 1 and Part 2 and the difference in the (follow-up – baseline) and (follow-up – fitting) values between Part 1 and Part 2 for all clinical measures except density of white blood cells.

Correlation analysis will be conducted for the change in CLDEQ score and the difference in the (follow-up – baseline) and (follow-up – fitting) values of all clinical measures except density of white blood cells between Part 1 and Part 2. Pearson product-moment correlation coefficient will be provided for continuous endpoints. For each of the primary endpoints, when there is more than one measurement taken for each subject, the mean will be used in the analysis and a test based on the corresponding correlation coefficient will be conducted separately. Tests for the relationship each of the endpoints will be conducted separately using two-sided 95% confidence intervals constructed for the corresponding correlation coefficient. The relationship of the endpoints will be concluded to be significant if 0 does not fall within confidence limits of the corresponding coefficient. The directional statistical relationship will be determined using the upper or lower limit of the 95% confidence interval. Upper limit below zero or lower limit above zero of the 95% confidence will determine negative or positive relationship, respectively, between the clinical measures.

4. For Part 1 and 2: at 14 hours, symptomatic subjects will have a greater change from baseline in all the clinical measures except density of white blood cells in the eyelid margins.

The analysis procedure will follow the exact steps for analyzing the change from baseline in mean as described in the primary analysis section for LMS, NIBUT, TMH, and TOSM except the response variable will be the change of LMS, NIBUT, TMH, and TOSM from the corresponding baseline and the covariate baseline LMS, NIBUT, TMH, and TOSM will be excluded from the model. Comparisons between subject strata will be carried out using a one-sided 95% CI of least-square means differences (symptomatic - asymptomatic) for the change form bassline for the hypothesis given below:

$$H_0: \mu_S - \mu_A \leq 0$$
$$H_A: \mu_S - \mu_A > 0,$$

where S=Symptomatic and A=Asymptomatic. A statistically greater change, on average, for symptomatic subjects compared to asymptomatic subjects will be concluded if the lower limit of the 95% confidence intervals for the Least-squares means is greater than 0.

Other observations will be presented in a separate laboratory protocol and will be analyzed in a separate report.

14.8. Interim Analysis

There will not be an interim read performed on this study.

14.9. Procedure for Handling Missing Data and Drop-Outs

Missing or spurious values will not be imputed. The count of missing values will be included in the summary tables and listings.

Subject dropout is expected to be one of the main reasons of missing data in this clinical trial. Past clinical trials don't provide the evidence that subject dropout is systematic or not-at-random. To evaluate the impact of missing data, sensitivity analysis will be conducted using multiple imputation methods if the proportion of subject dropout is greater than the 15%. The SAS/STAT procedures PROC MI and PROC MIANALYZE will be utilized with a parametric regression method used to make at least 50 imputations.

14.10. Procedure for Reporting Deviations from Statistical Plan

The analysis will be conducted according to that specified in above sections. There are no known reasons for which it is planned to deviate from these analysis methods. If for any reason a change is made, the change will be documented in the study report along with a justification for the change.

15. DATA HANDLING AND RECORD KEEPING/ARCHIVING

15.1. Electronic Case Report Form/Data Collection

The data for this study will be captured on electronic case report forms (eCRFs) using an EDC system (Bioclinica). An authorized data originator will enter study data into the eCRFs using the EDC system. Data collected on equipment that is not captured in EDC will be formatted to the specification of the JJVC database manager and sent to JJVC for analysis. Data generated from post hoc measurements (e.g. tear meniscus height, lid wiper image analysis, tear film cytokines, etc.) will be collected on specific Microsoft Office Excel format worksheets at the clinical site and at the completion of the analysis transferred to JJVC biostatistician for data analysis in such format.

The clinical data will be recorded on dedicated eCRFs specifically designed to match the study procedures for each visit. Once completed, the eCRFs will be reviewed for accuracy and completeness and signed by the Investigator. The sponsor or sponsor's representatives will be

authorized to gain access to the subject recordation for the purposes of monitoring and auditing the study.

Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection. Data will be transmitted from the clinical site to a secure central database as forms are completed or updated, ensuring information accuracy, security, and confidentiality. After the final database lock, the Investigator will be provided with Individual Patient Profiles (IPP) including the full audit trail on electronic media in PDF format for all of the study data. The IPP must be retained in the study files as a certified copy of the source data for the study.

The content and structure of the eCRFs are compliant with ISO14155:2011.[1]

15.2. Subject Record

At a minimum, subject record should be available for the following:

- subject identification
- eligibility
- study identification
- study discussion
- provision of and date of informed consent
- visit dates
- results of safety and efficacy parameters as required by the protocol
- a record of all adverse events
- follow-up of adverse events
- medical history and concomitant medication
- test article receipt/dispensing/return records
- date of study completion
- reason for early discontinuation of test article or withdrawal from the study, if applicable

The subject record is the eCRF or an external record. The author of an entry in the subject record must be identifiable. The first point of entry is considered to be the source record.

Adverse event notes must be reviewed and initialed by the Investigator.

16. DATA MANAGEMENT

16.1. Access to Source Data/Document

The Investigator/Institution will permit trial-related monitoring, audits, IEC/IRB review and regulatory inspection(s) by providing direct access to source data/documents. Should the clinical site be contacted for an audit by an IEC/IRB or regulatory authority, JJVC must be contacted and notified in writing within 24 hours.

16.2. Confidentiality of Information

Information concerning the investigational product and patent application processes, scientific data or other pertinent information is confidential and remains the property of JJVC. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that JJVC will use information developed in this clinical study in connection with the development of the investigational product and therefore may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

16.3. Data Quality Assurance

Steps will be taken to ensure the accuracy and reliability of data, include the selection of qualified investigators and appropriate clinical sites and review of protocol procedures with the Principal Investigator. The Principal Investigator, in turn, must ensure that all Sub-Investigators and clinical site personnel are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study article.

Training on case report form completion will be provided to clinical site personnel before the start of the study. The Sponsor will review case report forms for accuracy and completeness remotely during the conduct of the study, during monitoring visits, and after transmission to data management. Any data discrepancies will be resolved with the Investigator or designee, as appropriate.

Quality Assurance representatives from JJVC may visit clinical sites to review data produced during the study and to access compliance with applicable regulations pertaining to the conduct of clinical trials. The clinical sites will provide direct access to study-related source data/documents and reports for the purpose of monitoring and auditing by JJVC and for inspection by local and regulatory authorities.

17. MONITORING

The study monitors will maintain close contact with the Principal Investigator and the Investigator's designated clinical site personnel. The monitor's responsibilities will include:

- Ensuring that the investigation is being conducted according to the protocol, any subsequent amendments, and regulatory requirements are maintained
- Ensuring the rights and wellbeing of subjects are protected
- Ensuring adequate resources, including facilities, laboratories, equipment, and qualified clinical site personnel
- Ensuring that protocol deviations are documented with corrective action plans, as applicable
- Ensuring that the clinical site has sufficient test article and supplies
- Clarifying questions regarding the study
- Resolving study issues or problems that may arise

- Reviewing of study records and source documentation verification in accordance with the monitoring plan

18. ETHICAL AND REGULATORY ASPECTS

18.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. Subjects will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

18.2. Investigator Responsibility

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the signed agreement, the investigational plan, Section 4 of the ICH E6 guidelines on Good Clinical Practice (GCP),[2] and applicable regulatory requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles of the Declaration of Helsinki 64th WMA General Assembly 2013[3] and that the clinical study data are credible. The Investigator must maintain clinical study files in accordance with Section 8 of the ICH E6 guidelines on Good Clinical Practice (GCP),[2] and applicable regulatory requirements.

18.3. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the Investigator (or Sponsor when applicable) will provide the IEC/IRB with current and complete copies of the following documents (where applicable):

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruitment materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's curriculum vitae, clinical licenses, or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study, the Investigator (or Sponsor when applicable) will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruitment materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB)
- Reports of adverse events that are serious, unanticipated, and associated with the test articles, according to the IRB's requirements
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Major protocol deviations as required by the IEC/IRB
- Report of deaths of subjects under the Investigator's care
- Notification if a new Investigator is responsible for the study at the clinical site
- Any other requirements of the IEC/IRB

For protocol amendments that increase subject risk, the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will review and reapprove this clinical study. This request should be documented in writing.

At the end of the study, the Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion. Documentation of this notification must be retained at the clinical site and a copy provided to the CRO or Sponsor as applicable.

18.4. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and by the reviewing IEC/IRB. The informed consent is in accordance with principles that originated in the Declaration of Helsinki,[3] current ICH[2] and ISO 14155[1] guidelines, applicable regulatory requirements, and Sponsor Policy.

Before entry into the study, the Investigator or an authorized member of the clinical site personnel must explain to potential subject the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

18.5. Privacy of Personal Data

The collection, processing and disclosure of personal data and medical information related to the Study Subject, and personal data related to Principal Investigator and any clinical site personnel (e.g., name, clinic address and phone number, curriculum vitae) is subject to compliance with the General Data Protection Regulation[7], UK Data Protection Act 2018[8] and other applicable personal data protection and security laws and regulations. Appropriate measures will be employed to safeguard these data, to maintain the confidentiality of the person's related health and medical information, to properly inform the concerned persons about the collection and processing of their personal data, to grant them reasonable access to their personal data and to prevent access by unauthorized persons.

All information obtained during the course of the investigation will be regarded as confidential. All personal data gathered in this trial will be treated in strictest confidence by Investigators, monitors, Sponsor's personnel and IEC/IRB. No data will be disclosed to any third party without the express permission of the subject concerned, with the exception of Sponsor personnel (monitor, auditor), IEC/IRB and regulatory organizations in the context of their investigation related activities that, as part of the investigation will have access to the CRFs and subject records.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.
The Sponsor ensures that the personal data will be:

- processed fairly and lawfully
- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.

The subject has the right to request through the Investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

19. STUDY RECORD RETENTION

In compliance with the ICH/GCP guidelines,[2] the Investigator/Institution will maintain all CRFs and all subject records that support the data collected from each subject, as well as all study documents as specified in ICH/GCP[2] and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or instructed by the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.
If the Investigator has a question regarding retention of study records, he/she should contact JJVC.

20. FINANCIAL CONSIDERATIONS

Remuneration for study services and expenses will be set forth in detail in the Clinical Research Agreement. The Research Agreement will be signed by the Principal Investigator and a JJVC management representative prior to study initiation.

JJVC reserves the right to withhold remuneration for costs associated with protocol violations such as:

- Continuing an ineligible subject in the study
- Scheduling a study visit outside the subject's acceptable visit range

JJVC reserves the right to withhold final remuneration until all study related activities have been completed, such as:

- Query resolution
- Case Report Form signature
- Completion of any follow-up action items

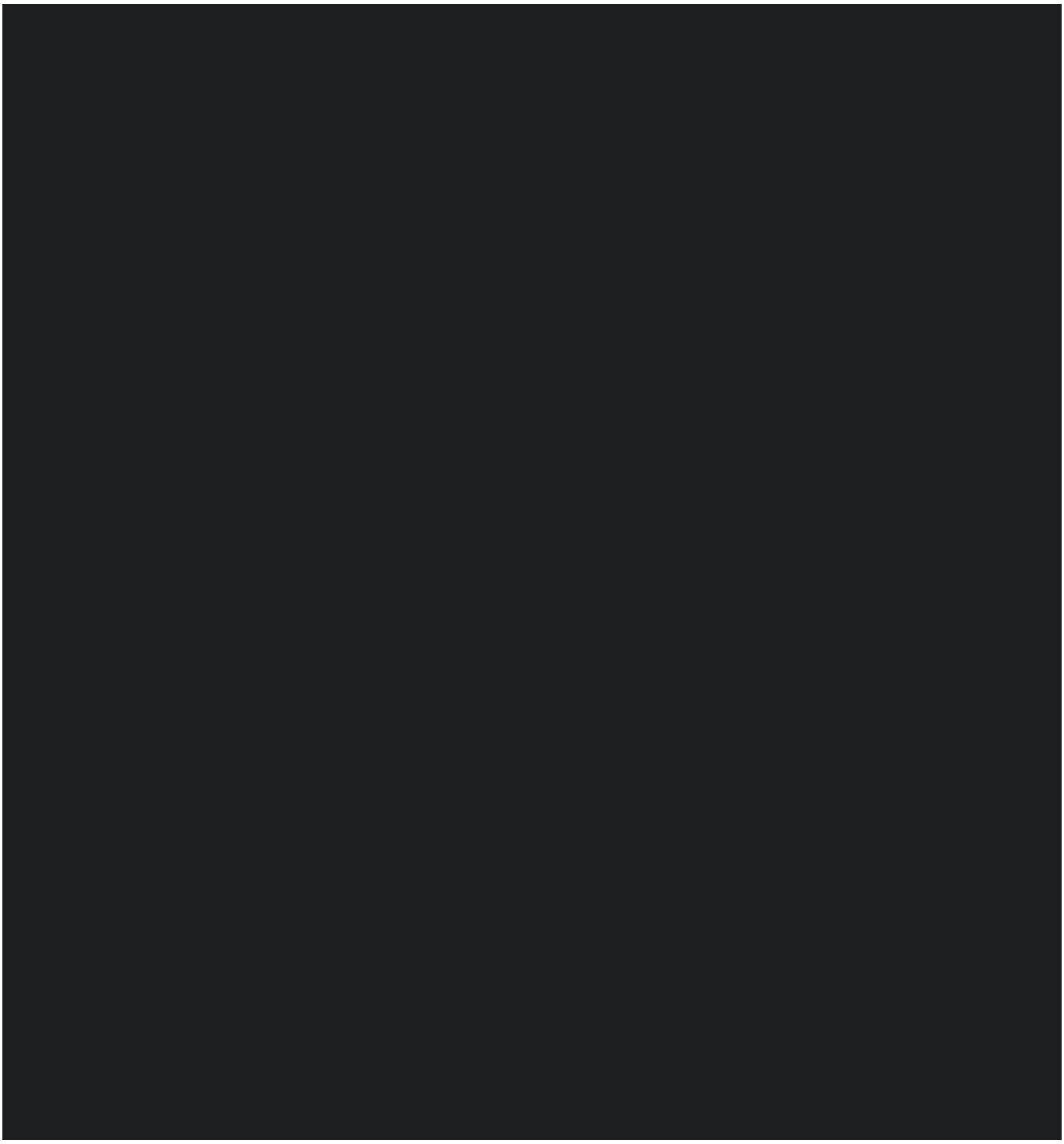
21. PUBLICATION

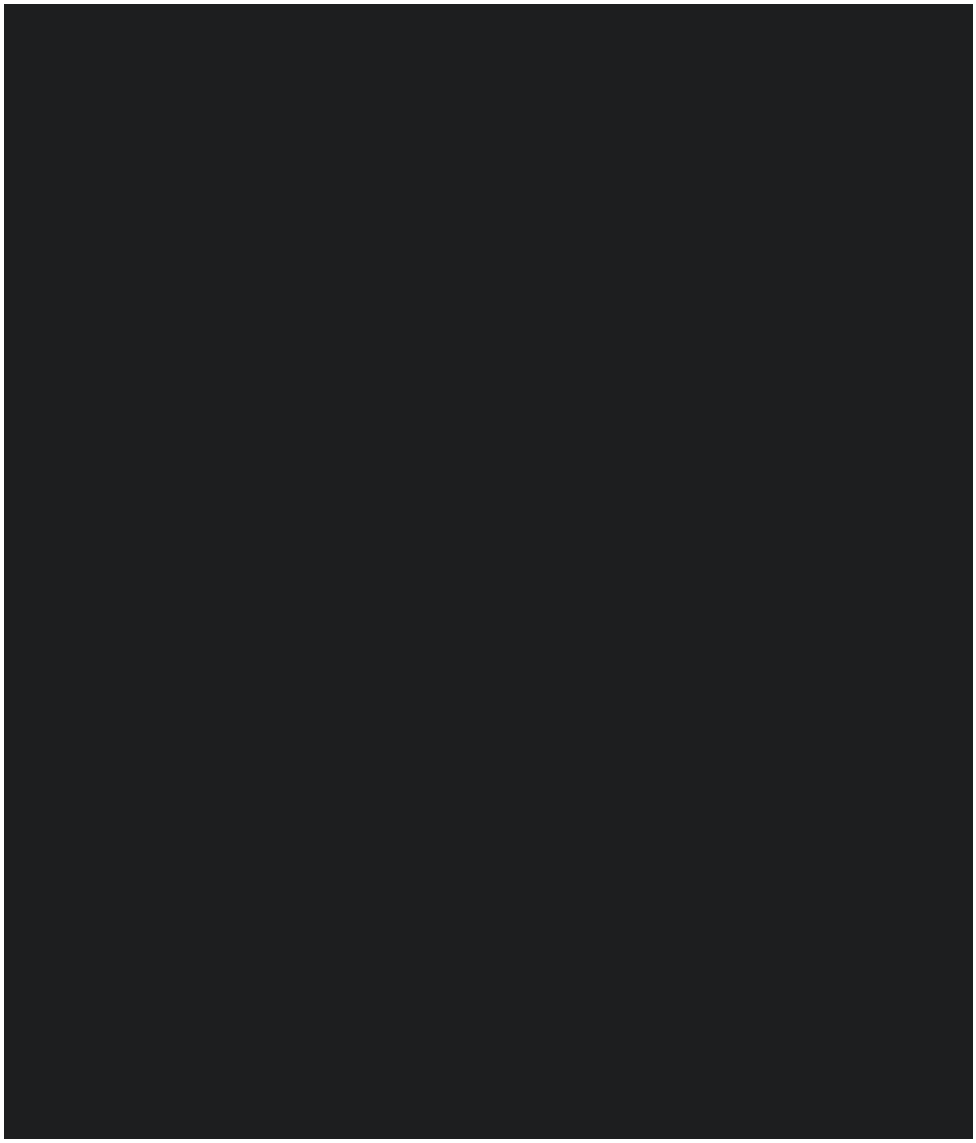
This study will be registered on ClinicalTrials.gov by the study sponsor.

22. REFERENCES

1. ISO 14155:2011: Clinical Investigation of Medical Devices for Human Subjects — Good Clinical Practice. Available at: https://www.iso.org/standard/45557.html
2. International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP). Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
3. Declaration of Helsinki - Ethical principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
4. United States (US) Code of Federal Regulations (CFR). Available at: https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
5. Navascues-Cornago M. [redacted] *Clinical study report version 1.0: End-of-Day clinical assessment of asymptomatic and symptomatic soft contact lens wearers.* April 6, 2018.
6. Morgan PB. [redacted] *Clinical study report version 1.0: Confocal microscopy of the eyelid margin as a surrogate for contact lens discomfort.* June 12, 2018.
7. General Data Protection Regulation. Available at: https://www.eugdpr.org/
8. *Data Protection Act. Available at:* http://www.legislation.gov.uk/ukpga/2018/12/contents/enacted
9. http://www.legislation.gov.uk/ukpga/2018/12/contents/enacted
10. Keselman H, Algina J, Kowalchuk RK, Wolfinger RD. A comparison of two approaches for selecting covariance structures in the analysis of repeated measurements. *Communications in Statistics-Simulation and computation.* 1998;27(3):591-604.
11. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*. 1997:983-997.
12. Kenward MG, Roger JH. An improved approximation to the precision of fixed effects from restricted maximum likelihood. *Computational Statistics & Data Analysis.* 2009;53(7):2583-2595.
13. Edwards D, Berry JJ. The efficiency of simulation-based multiple comparisons. *Biometrics*. 1987:913-928.

APPENDIX A: PATIENT REPORTED OUTCOMES (STUDY QUESTIONNAIRES)





APPENDIX B: PATIENT INSTRUCTION GUIDE

The Patient Instruction Guide will be provided separately.

APPENDIX C: PACKAGE INSERT (APPROVED PRODUCT)

Dailies AquaComfort Plus

Acuvue Oasys 1-Day

Alcon®
a Novartis company

FOCUS® DAILIES®, FOCUS® DAILIES® Toric, FOCUS® DAILIES® Progressives, DAILIES® AquaComfort Plus®, DAILIES® AquaComfort Plus® Toric and DAILIES® AquaComfort Plus® Multifocal (nelfilcon A) One-Day Contact Lenses

92024162

IMPORTANT: This package insert is effective as of October, 2013 and supersedes all prior inserts for the product described below. Please read carefully and keep this information for future use. This package insert is intended for the eye care professional, but should be made available to patients upon request. The eye care professional should provide the patient with appropriate instructions that pertain to the patient's prescribed lenses. Copies of this package insert are available without charge from Alcon by calling Customer Service at 1-800-241-5999 or download from our website at www.alcon.com. In addition a Patient Instruction Booklet is available which is recommended to be given to patients.

Rx only

CAUTION: FEDERAL LAW (USA) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A LICENSED EYE CARE PROFESSIONAL.

DESCRIPTION

FOCUS® DAILIES® and DAILIES® AquaComfort Plus® (nelfilcon A) Soft (hydrophilic) One-Day Contact Lenses are available in a spherical lens design. FOCUS® DAILIES® Toric and DAILIES® AquaComfort Plus® Toric (nelfilcon A) Soft (hydrophilic) One-Day Contact Lenses are available in a toric design. FOCUS® DAILIES® Progressives and DAILIES® AquaComfort Plus® Multifocal (nelfilcon A) Soft (hydrophilic) One-Day Contact Lenses are available in a multifocal lens design. The lenses are to be prescribed for single use, daily disposable wear.

LENS MATERIAL

The lens material is 69% water and 31% nelfilcon A polymer (polyvinyl alcohol partially acetalized with N-formylmethyl acrylamide).

- For VISITINT® lenses, the color additive copper phthalocyanine is added to the lens material to create a light blue edge to edge color to make them easier to see when handling.
- Print marks on FOCUS® DAILIES® Toric and DAILIES® AquaComfort Plus® Toric (nelfilcon A) contact lenses contain the color additive phthalocyanine green.

LENS PROPERTIES

- Refractive index: 1.38 (hydrated)
- Light transmittance: VISITINT® ≥ 92% (@ 610 nm)
- Oxygen permeability (Dk): 26 x 10 -11 (cm2/sec) (ml O2 /ml x mm Hg), measured at 35°C (Fatt, edge effect corrected)
- Water content: 69% by weight in normal saline

Approved Power Range: -20.00D to +20.00D

LENS PARAMETERS[1]

FOCUS® DAILIES® (nelfilcon A) One-Day Contact Lenses are available in the following dimensions:

- Base curve: 8.6 mm
- Diameter: 13.8 mm
- Powers available: -0.50D to -6.00D (0.25D steps); -6.50D to -10.00D (0.50D steps); +0.50D to +6.00D (0.25D steps)
- Center thickness: 0.10 mm at -3.00D (varies with power)
- Tint: Light blue handling tint

FOCUS® DAILIES® Toric (nelfilcon A) One-Day Contact Lenses are available in the following dimensions:

- Base curve: 8.6 mm
- Diameter: 14.2 mm
- Powers available: +4.00D to -6.00D (0.25D steps) -6.50D to -8.00D (0.50D steps) Cylinder: -0.75D, -1.50D Axis: 20°, 70°, 90°, 110°, 160°, 180°
- Center thickness: 0.10 mm at -3.00D (varies with power)
- Tint: Light blue handling tint

FOCUS® DAILIES® Progressives (nelfilcon A) One-Day Contact Lenses are available in the following dimensions:

- Base curve: 8.6 mm
- Diameter: 13.8 mm
- Powers available: +5.00D to -6.00D (0.25D steps) Single Progressive Add Effective Range up to +3.00D
- Center thickness: 0.11 mm at -3.00D (varies with power)
- Tint: Light blue handling tint

DAILIES® AquaComfort Plus® (nelfilcon A) One-Day Contact Lenses are available in the following dimensions:

- Base curve: 8.7 mm
- Diameter: 14.0 mm
- Powers available: -0.50D to -6.00D (0.25D steps); -6.50D to -10.00D (0.50D steps); +0.50D to +6.00D (0.25D steps)
- Center thickness: 0.10 mm at -3.00D (varies with power)
- Tint: Light blue handling tint

DAILIES® AquaComfort Plus® Toric (nelfilcon A) One-Day Contact Lenses are available in the following dimensions:

- Base curve: 8.8 mm
- Diameter: 14.4 mm
- Powers available: +4.00D to -6.00D (0.25D steps); -6.50D to -8.00D (0.50D steps); Cylinder: -0.75D, -1.25D, -1.75D Axis: 10°, 20°, 70°, 80°, 90°, 100°, 110°, 160°, 170°, 180°
- Center thickness: 0.10 mm at -3.00D (varies with power)
- Tint: Light blue handling tint

DAILIES® AquaComfort Plus® Multifocal (nelfilcon A) One-Day Contact Lenses are available in the following dimensions:

- Base curve: 8.7 mm
- Diameter: 14.0 mm
- Powers available: +6.00D to -10.00D (0.25D steps); ADD: LO, MED, HI
- Center thickness: 0.10 mm at -3.00D (varies with power)
- Tint: Light blue handling tint

Hereafter, FOCUS® DAILIES®, FOCUS® DAILIES® Toric, FOCUS® DAILIES® Progressives, DAILIES® AquaComfort Plus®, DAILIES® AquaComfort Plus® Toric and DAILIES® AquaComfort Plus® Multifocal (nelfilcon A) One-Day Contact Lenses will be referred to as DAILIES® (nelfilcon A) One-Day Contact Lenses unless product distinction is necessary.

ACTIONS

- When hydrated and placed on the cornea DAILIES® (nelfilcon A) One-Day Contact Lenses act as a refracting medium to focus light rays on the retina.

INDICATIONS (Uses)

- FOCUS® DAILIES® and DAILIES® AquaComfort Plus® (nelfilcon A) One-Day Contact Lenses are indicated for daily wear for the optical correction of refractive ametropia (myopia and hyperopia) in not-aphakic persons with non-diseased eyes with up to approximately 1.50 diopters (D) of astigmatism that does not interfere with visual acuity.
- FOCUS® DAILIES® Toric, and DAILIES® AquaComfort Plus® Toric (nelfilcon A) One-Day Contact Lenses are indicated for daily wear for the optical correction of refractive ametropia (myopia and hyperopia) in not-aphakic persons with non-diseased eyes with 6.00 diopters (D) or less of astigmatism.
- FOCUS® DAILIES® Progressives and DAILIES® AquaComfort Plus® Multifocal (nelfilcon A) One-Day Contact Lenses are indicated for daily wear for the optical correction of refractive ametropia (myopia or hyperopia) and/or presbyopia in not-aphakic persons with non-diseased eyes who require a reading addition of +3.00 diopters (D) or less and who may have 1.50 diopters (D) or less of astigmatism that does not interfere with visual acuity.
- DAILIES® (nelfilcon A) One-Day Contact Lenses are to be prescribed for single use, daily disposable wear. The lenses are not intended to be cleaned or disinfected and should be discarded after a single use.

CONTRAINDICATIONS (Reasons not to use)

Do not use DAILIES® (nelfilcon A) One-Day Contact Lenses when any of the following conditions exists:

- Acute or subacute inflammation or infection of the anterior chamber of the eye.
- Any eye disease, injury or abnormality affecting the cornea, conjunctiva, or eyelids that may be exacerbated by contact lens wear.
- Insufficiency of lacrimal secretion (dry eye) that interferes with contact lens wear.
- Corneal hypoesthesia (reduced corneal sensitivity).
- Any systemic disease which may be exacerbated by or interferes with contact lens wear.
- Allergic reactions of ocular irritation of the ocular surfaces or adnexa that may be caused by or exacerbated by the wearing of contact lenses.
- Ocular irritation due to allergic reactons which may be caused by use of contact lens solutions (i.e., rewetting drops) that contain chemicals or preservatives (such as thimerosal) to which some people may develop an allergic response.
- Any active corneal infection (bacterial, fungal, or viral).
- The use of any medication that is contraindicated or interferes with contact lens wear, including eye medications.
- Patient history of recurring eye or eyelid infections, adverse effects associated with contact lens wear, intolerance or abnormal ocular response to contact lens wear.
- If eyes become red or irritated.

WARNINGS

Patients should be advised of the following warnings pertaining to contact lens wear:

- Problems with contact lenses and lens care products could result in serious injury to the eye. It is essential that patients follow their eye care professional's directions and all labeling instructions for proper use of their lenses. **Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision.**
- Daily wear lenses are not indicated for overnight wear, and patients should be instructed not to wear lenses while sleeping. Clinical study results[2] have shown that the risk of ulcerative keratitis is nine times greater for daily wear users who wear their lenses overnight (outside the approved indication) compared to those who do not wear them overnight.
- Studies[2] have shown that contact lens wearers who smoke have an estimated 3 to 8 times greater risk of suffering ulcerative keratitis than those who are nonsmokers.
- If a patient experiences eye discomfort, excessive tearing, vision changes, redness of the eye, or other problems they should be instructed to immediately remove their lenses and promptly contact their eye care professional. It is recommended that contact lens wearers see their eye care professional regularly as directed.

PRECAUTIONS

Special Precautions for the Eye Care Professional:

Due to the small number of patients enrolled in the clinical investigation of lenses, all refractive powers, design configurations, or lens parameters available in the lens material are not evaluated in significant numbers. Consequently, when selecting an appropriate lens design and parameters, the eye care professional should consider all characteristics of the lens that can affect lens performance and ocular health, including oxygen permeability, central and peripheral thickness, and optic zone diameter.

The potential impact of these factors on the patient's ocular health should be carefully weighed against the patient's need for refractive correction; therefore, the continuing ocular health of the patient and lens performance on the eye should be carefully monitored by the prescribing eye care professional.

- Fluorescein, a yellow dye, should not be used while the lenses are on the eyes. The lenses absorb this dye and become discolored. Whenever fluorescein is used, the eyes should be flushed thoroughly with sterile saline solution that is recommended for in eye use prior to inserting lenses. Avoid dispensing saline from an aerosol can directly into the eye.
- Patients who wear contact lenses to correct presbyopia may not achieve the best corrected visual acuity for either far or near vision. Visual requirements vary with the individual and should be considered when selecting the most appropriate type of lens for each patient.
- Before leaving the eye care professional's office, the patient should be able to promptly remove their lenses or should have someone else available who can remove their lenses for them.
- Eye care professionals should instruct the patient to remove the lenses immediately if the eye becomes red or irritated.
- Routine eye examinations are necessary to help assure the continuing health of the patient's eyes. Eye care professionals should make arrangements with the patient for appropriate follow-up visits. Alcon recommends that patients see their eye care professional once each year or as recommended by the eye care professional.
- Visual changes or changes in lens tolerance may occur during pregnancy or use of oral contraceptives. Caution patients accordingly.

Eye Care Professionals should carefully instruct patients about the following safety precautions:

- Carefully follow the handling, insertion, removal, and wearing instructions in the DAILIES® (nelfilcon A) One-Day Contact Lenses Patient Instruction Booklet and any additional instructions provided by the eye care professional.
- Note the correct lens power for each eye to prevent getting them mixed up.
- Always keep spare lenses available to avoid reusing the lenses.
- Good hygiene habits help promote safe and comfortable lens wear. Always wash and rinse hands before handling lenses.
- Shake the blister pack gently prior to opening. Remove the lens from the blister pack by carefully pouring the lens onto the palm of your clean hand.
- Never use tweezers or other sharp objects such as fingernails to remove the lens from the container to avoid damaging the lens.
- Eye irritation, infection, or lens damage may result if cosmetics, lotion, soap, cream, hair spray, deodorant, aerosol products or foreign particles come in contact with lenses. If sprays are used, eyes should be kept closed until the spray has settled.
- Always handle lenses carefully. If a lens is dropped, small particles or fibers may adhere to the lens surface which can irritate the eye. Replace with a sterile fresh, new lens.
- Never allow contact lenses to come into contact with non-sterile liquids (including tap water and saliva) as microbial contamination can occur, which may lead to permanent eye damage.
- Consult the eye care professional about wearing lenses during sporting and water related activities. Exposure to water while wearing contact lenses in activities such as swimming, water skiing, and hot tubs may increase the risk of ocular infection, including but not limited to Acanthamoeba keratitis.
- Avoid all harmful or irritating vapors or fumes while wearing lenses.
- Promptly remove a lens to avoid serious injury in the event that dust, a foreign body or other contaminant gets between the lens and the eye.
- Discard any lens which has become dehydrated or damaged. Replace with a sterile fresh, new lens.
- Patients should be instructed to remove their lenses before sleeping.
- The lens should move freely on the eye at all times. If the lens sticks (stops moving) on the eye, follow the recommended directions in the section Care for a Sticking Lens. If non-movement of the lens continues, the patient should be instructed to consult their eye care professional immediately.
- Patients should inform their employer of being a contact lens wearer. Some jobs may require the use of eye protection equipment or restrict the use of contact lenses in certain work environments.
- Patients should inform their physician that contact lenses are worn and should consult their eye care professional before using any medication in the eye.
- Do not use lenses beyond the expiration date.
- Certain medications such as antihistamines, decongestants, diuretics, muscle relaxants, tranquilizers, and those for motion sickness may cause dryness of the eye, increased lens awareness, lens intolerance, blurred vision or visual changes. Patients should be informed of these potential conditions and proper remedial treatment should be prescribed if any of these conditions occur. Depending on the severity of the condition appropriate treatment may include the use of rewetting drops intended for use with soft contact lenses or temporary cessation of contact lens wear until the conditions subsides.

It is strongly recommended that patients be provided with a copy of the DAILIES® (nelfilcon A) One-Day Contact Lenses Patient Instruction Booklet available from Alcon Laboratories and understand its contents prior to dispensing the lenses.

ADVERSE REACTIONS

Potentially serious complications are usually accompanied by one or more of the following signs or symptoms:

- Foreign body sensation
- Excessive watering or other unusual eye secretions including mucopurulent discharge
- Redness of the eyes
- Photophobia (sensitivity to light)
- Burning, stinging, itching or other pain associated with the eyes
- Comfort is less compared to when the lens was first placed on eye
- Poor visual acuity (reduced sharpness of vision)
- Blurred vision, rainbows or halos around objects
- Feeling of dryness

If any of the previous signs or symptoms occur:

- **The patient should IMMEDIATELY REMOVE THE LENS(ES). If the discomfort or problem stops, the patient should discard the lens and replace it with a new one. IF THE PROBLEM CONTINUES AFTER INSERTING A NEW LENS, THE PATIENT SHOULD IMMEDIATELY REMOVE THE LENS(ES) AND CONTACT AN EYE CARE PROFESSIONAL AT ONCE**
- Patients should be informed that a serious condition such as corneal ulcer, infection, corneal vascularization, or iritis may be present and may progress rapidly. Less serious reactions such as abrasions, infiltrates and bacterial conjunctivitis must be managed and treated early to avoid more serious complications. Additionally, contact lens wear may be associated with ocular changes which require consideration of discontinuation or restriction of wear. These include but are not limited to local or generalized corneal edema, epithelial microcysts, epithelial staining, infiltrates, neovascularization, endothelial polymegathism, tarsal papillary changes, conjunctival injection or iritis.

ADVERSE REACTION REPORTING

If a patient experiences any serious adverse effects associated with the use of DAILIES® (nelfilcon A) One-Day Contact Lenses, licensed eye care professionals please notify: Alcon Medical Safety in the USA at 1-800-241-7468.

FITTING

For a detailed description of the fitting techniques, refer to the DAILIES® (nelfilcon A) One-Day Contact Lenses Professional Fitting and Information Guide, copies of which are available free of charge from:

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX, USA 76134
1-800-241-5999

REPLACEMENT AND WEAR SCHEDULE

DAILIES® (nelfilcon A) One-Day Contact Lenses are intended to be worn once and then discarded at the end of each wearing period. The patient should be instructed to start the next wearing period with a fresh new lens.

WEARING SCHEDULE

- **Daily Wear (less than 24 hours, while awake)**
  The maximum daily wearing time should be determined by the eye care professional based upon the patient's physiological eye condition because individual responses to contact lenses vary. There may be a tendency for patients to overwear the lenses initially. The eye care professional should stress the importance of adhering to the initial maximum wearing schedule. Studies have not been conducted to show that DAILIES® (nelfilcon A) One-Day Contact Lenses are safe to wear during sleep, therefore patients should be advised to remove their lenses while sleeping. Normal daily wear of lenses assumes a minimum of 6 hours of non-lens wear per 24 hour period. Optimum individual wearing schedule will vary.

CLINICAL DETAILS

- **Seasonal Allergy Wearers**
  A one month subjective trial of contact lens wearers with a history of seasonal allergic conjunctivitis was conducted during a month of expected high pollen count in various US cities. Information was collected about allergy-related symptoms, wear-time and comfort during lens wear. Study results found that these contact lens wearers experienced fewer days of burning and redness when wearing FOCUS® DAILIES® contact lenses as compared to a new pair of their usual lenses. The effects of allergy medications that may have been used during the study were not assessed.
- **All Day Comfort**
  A one month study of 188 subjects was conducted for the purpose of evaluating comfort and wearing time for FOCUS® DAILIES® soft contact lenses. End of day comfort was measured using a 0 to 10 scale where 0 was unacceptable and 10 was excellent. Wearing time was also recorded in hours of wear per day.

Baseline values for end of day comfort and average wearing time with the subject's pre-study lenses were 6.9 out of 10 and 13.5 hours, respectively. Study results found that the average end of day comfort for FOCUS® DAILIES® contact lenses was 7.8 out of 10 with an average wearing time of 14.3 hours. The values for FOCUS® DAILIES® were statistically different compared to the baseline values collected from the pre-study lenses. As in this study, individual results may vary.

Reference: Bauman, E. (1997). Daily Disposables Versus Other Soft Lens Modalities. Optician 214: 33-35, 37.

- **DAILIES® AquaComfort Plus®**
  A one-month study was conducted for the purpose of evaluating the performance for DAILIES® AquaComfort Plus® lenses. Subjective performance measures were evaluated by having the subjects rate these attributes on a scale from 1 to 10, where 1 was "poor/not at all satisfied" and 10 was "excellent/completely satisfied," for both their previous FOCUS® DAILIES® lenses as well as DAILIES® AquaComfort Plus® lenses.

  Subjects rated DAILIES® AquaComfort Plus® contact lenses statistically better for comfort at insertion compared to their own FOCUS® DAILIES® / All Day Comfort lenses. Specifically, average comfort at insertion was 9.0 at baseline with FOCUS® DAILIES® lenses and was 9.5 at one-month with DAILIES® AquaComfort Plus® lenses. Additionally, average overall comfort was 8.8 at baseline with FOCUS® DAILIES® and was 9.1 at one-month with DAILIES® AquaComfort Plus®, while the average comfort at the end of the day was 7.8 at baseline with FOCUS® DAILIES® lenses and was 8.5 at one-month with DAILIES® AquaComfort Plus® lenses (changes not statistically significant).

EMERGENCY LENS CARE

Cleaning and disinfection of the lens is not recommended. The patient should be reminded to have replacement lenses or back-up spectacles available at all times.

CARE FOR A STICKING OR TORN LENS

If the lens sticks (stops moving) or cannot be removed from the eye, instruct the patient to apply 1 to 2 drops of a recommended lubricating or rewetting solution in accordance with the manufacturer's instruction for use package labeling. The patient should blink forcefully several times, then while looking up slide the lens down onto the white part of the eye and remove the lens by pinching it between the thumb and forefinger. If the lens continues to stick, the patient should immediately consult the eye care professional.

If the lens tears in your eye it will feel uncomfortable. Advise patients it is not possible to lose a contact lens or part of a contact lens behind the eye and that they should calmly remove the pieces by carefully pinching them as they would do for normal lens removal. If the lens pieces do not seem to remove easily the eye may be rinsed with sterile saline. Excessive pinching should be avoided. If rinsing with saline does not help, instruct patients to contact the eye care professional for assistance. Lenses can be easily located by the eye care professional using fluorescein.

EMERGENCIES

Patients should be informed that if chemicals of any kind (household products, gardening solutions, laboratory chemicals, etc.) are splashed into the eyes, the patient should: **Flush eyes immediately with tap water or fresh saline solution, remove and discard the lens, and immediately contact the eye care professional or visit a hospital emergency room without delay.**

Additional information regarding emergency treatment may be provided on the product container label.

HOW SUPPLIED

DAILIES® (nelfilcon A) One-Day Contact Lenses are packaged in strips of five foil sealed blister packs containing phosphate-acetate buffered saline solution and are steam sterilized STERILE. Five blister pack containers are attached to form a single strip. The package storage saline may contain up to 0.05% Poloxamer. In addition, the package storage saline for DAILIES® AquaComfort Plus®, DAILIES® AquaComfort Plus® Toric and DAILIES® AquaComfort Plus® Multifocal One-Day Contact Lenses contains polyethylene glycol (PEG) and hydroxypropyl methylcellulose (HPMC). The package is marked with the base curve, diameter, dioptric power, manufacturing lot number and expiration date.

The following may appear on the labels or cartons:

Symbols/Signs	Description
Rx only	CAUTION: Federal (United States) law restricts this device to sale by or on the order of a licensed eye care professional.
STERILE	Steam sterilized
EXP	Use by date (Expiry date)
LOT	Batch code
en	Example of two letter language code (English)
Do Not Reuse	Do Not Reuse
DIA	Diameter
BC	Base curve
PWR	Lens power
LO	"Low" near ADD
MED	"Medium" near ADD
HI	"High" near ADD
CE 0086	European conformity sign
	See product instructions
EC REP	Authorized Representative European Community
	Manufacturer
	Packaging waste license sign

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX
76134-2099, USA

Alcon®
a Novartis company

[1]Check for actual product availability as additional powers may be introduced over time.
[2]New England Journal of Medicine, September 21, 1989; 321 (12), pp.773-783.

IMPORTANT: Please read carefully and keep this information for future use.

This Package Insert and Fitting Guide is intended for the Eye Care Professional, but should be made available to patients upon request.

The Eye Care Professional should provide the patient with the appropriate instructions that pertain to the patient's prescribed lenses. Copies are available for download at www.acuvue.com.

ACUVUE® 1-Day
oasys WITH HydraLuxe™
BRAND CONTACT LENSES

ACUVUE OASYS® Brand Contact Lenses 1-Day with HydraLuxe™ Technology

ACUVUE OASYS® Brand Contact Lenses 1-Day with HydraLuxe™ Technology for ASTIGMATISM

senofilcon A Soft (hydrophilic) Contact Lenses Visibility Tinted with UV Blocker for Daily Disposable Wear

℞ Only CAUTION: U.S. Federal law restricts this device to sale by or on the order of a licensed practitioner.

SYMBOLS KEY

The following symbols may appear on the label or carton:

SYMBOL	DEFINITION
	Consult Instructions for Use
	Manufactured by or in
	Date of Manufacture
	Use By Date (expiration date)
LOT	Batch Code
STERILE 	Sterile Using Steam or Dry Heat
	Single-Use
DIA	Diameter
BC	Base Curve
D	Diopter (lens power)
CYL	Cylinder
AXIS	Axis
CE 0086	Quality System Certification Symbol
 UV Blocking	UV-Blocking
	Fee Paid for Waste Management
 Only	CAUTION: U.S. Federal law restricts this device to sale by or on the order of a licensed practitioner
	Lens Orientation Correct
	Lens Orientation Incorrect (Lens Inside Out)

DESCRIPTION

ACUVUE OASYS® Brand Contact Lenses 1-Day and ACUVUE OASYS® Brand Contact Lenses 1-Day for ASTIGMATISM are soft (hydrophilic) contact lenses made with HydraLuxe™ Technology. They are available as spherical or toric lenses respectively.

These lenses are made of a silicone hydrogel material containing an internal wetting agent, visibility tint, and UV absorbing monomer and are tinted blue using Reactive Blue Dye #4 to make the lenses more visible for handling.

A benzotriazole UV absorbing monomer is used to block UV radiation. The transmittance characteristics for these lenses are less than 1% in the UVB range of 280 nm to 315 nm and less than 10% in the UVA range of 316 nm to 380 nm for the entire power range.

Lens Properties:

The physical/optical properties of the lens are:

- Specific Gravity (calculated): 0.98 - 1.12
- Refractive Index: 1.42
- Light Transmission: 85% minimum
- Surface Character: Hydrophilic
- Water Content: 38%
- Oxygen Permeability:

VALUE	METHOD
122 x 10^{-11} (cm^2/sec) (ml O_2/ml x mm Hg) at 35°C	Fatt (boundary corrected, non-edge corrected)
103 x 10^{-11} (cm^2/sec) (ml O_2/ml x mm Hg) at 35°C	Fatt (boundary corrected, edge corrected)

Lens Parameters:

- Diameter Range: 12.0 mm to 15.0 mm
- Center Thickness: varies with power
- Base Curve Range: 7.85 mm to 10.00 mm
- Spherical Power Range: -20.00D to +20.00D
- Cylinder Power Range: -0.25D to -10.00D
- Axis Range: 2.5° to 180°

AVAILABLE LENS PARAMETERS

ACUVUE OASYS® Brand 1-Day with HydraLuxe™ Technology are hemispherical shells of the following dimensions:

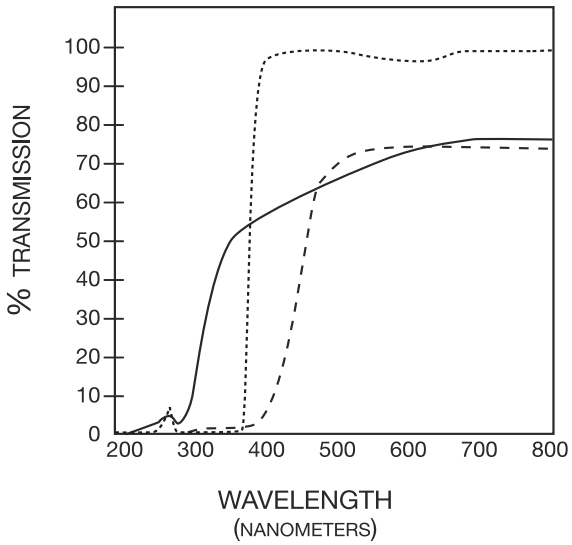
Diameter:	14.3 mm
Center Thickness:	0.085 mm to 0.221 mm (varies with power)
Base Curve:	8.5 mm, 9.0 mm
Powers:	-0.50D to -6.00D (in 0.25D increments) -6.50D to -12.00D (in 0.50D increments) +0.50D to +6.00D (in 0.25D increments) +6.50D to +8.00D (in 0.50D increments)

ACUVUE OASYS® Brand 1-Day with HydraLuxe™ Technology for ASTIGMATISM are hemitoric shells of the following dimensions:

Diameter:	14.3 mm
Center Thickness:	0.075 mm to 0.172 mm (varies with power)
Base Curve:	8.5 mm
Powers:	+0.00D to -6.00D (in 0.25D increments) Cylinders: -0.75D, -1.25D, -1.75D, -2.25D* Axis: 10° to 180° in 10° increments *-2.25D cylinder is availble in 10°, 20°, 70°, 80°, 90°, 100°, 110°, 160°, 170°, 180° axes only. +0.25D to +4.00D (in 0.25D increments) -6.50D to -9.00D (in 0.50D increments) Cylinders: -0.75D, -1.25D, -1.75D Axis: 10°, 20°, 70°, 80°, 90°, 100°, 110°, 160°, 170°, 180°

TRANSMITTANCE CURVES

ACUVUE OASYS® 1-Day with HydraLuxe™ Technology (senofilcon A) Visibility Tinted with UV Blocker vs. 24 yr. old human cornea and 25 yr. old human crystalline lens.



ACUVUE OASYS® 1-Day with HydraLuxe™ Technology (senofilcon A)*

24 YR. OLD HUMAN CORNEA[1]

25 YR. OLD HUMAN CRYSTALLINE LENS[2]

* The data was obtained from measurements taken through the central 3-5 mm portion for the thinnest marketed lens (-9.00D lens, 0.075 mm center thickness).

[1]Lerman, S., Radiant Energy and the Eye, MacMillan, New York, 1980, p. 58, figure 2-21

[2]Waxler, M., Hitchins, V.M., Optical Radiation and Visual Health, CRC Press, Boca Raton, Florida, 1986, p. 19, figure 5

WARNING: UV absorbing contact lenses are NOT substitutes for protective UV absorbing eyewear, such as UV absorbing goggles or sunglasses because they do not completely cover the eye and surrounding area. The patient should continue to use UV absorbing eyewear as directed.

ACTIONS

In its hydrated state, the contact lens, when placed on the cornea, acts as a refracting medium to focus light rays onto the retina.

The transmittance characteristics for these lenses are less than 1% in the UVB range of 280 nm to 315 nm and less than 10% in the UVA range of 316 nm to 380 nm for the entire power range.

NOTE: Long-term exposure to UV radiation is one of the risk factors associated with cataracts. Exposure is based on a number of factors such as environmental conditions (altitude, geography, cloud cover) and personal factors (extent and nature of outdoor activities). UV-Blocking contact lenses help provide protection against harmful UV radiation. However, clinical studies have not been done to demonstrate that wearing UV-Blocking contact lenses reduces the risk of developing cataracts or other eye disorders. The Eye Care Professional should be consulted for more information.

INDICATIONS (USES)

ACUVUE OASYS® Brand Contact Lenses 1-Day with HydraLuxe™ Technology are indicated for daily disposable wear for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes who may have 1.00D or less of astigmatism.

ACUVUE OASYS® Brand Contact Lenses 1-Day with HydraLuxe™ Technology for ASTIGMATISM are indicated for daily disposable wear for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes who may have 0.50D to 3.00D of astigmatism.

These lenses contain a UV Blocker to help protect against transmission of harmful UV radiation to the cornea and into the eye.

CONTRAINDICATIONS (REASONS NOT TO USE)

DO NOT USE these contact lenses when any of the following conditions exist:

- Acute or subacute inflammation or infection of the anterior chamber of the eye.
- Any eye disease, injury or abnormality that affects the cornea, conjunctiva, or eyelids.
- Severe insufficiency of lacrimal secretion (dry eye).

- Corneal hypoesthesia (reduced corneal sensitivity).
- Any systemic disease that may affect the eye or be exaggerated by wearing contact lenses.
- Allergic reactions of ocular surfaces or adnexa that may be induced or exaggerated by wearing contact lenses or use of contact lens solutions.
- Ocular irritation due to allergic reactions which may be caused by use of contact lens solutions (i.e., rewetting drops) that contain chemicals or preservatives (such as mercury, Thimerosal, etc.) to which some people may develop an allergic response.
- Any active corneal infection (bacterial, fungal, protozoal, or viral).
- If eyes become red or irritated.

WARNINGS

Patients should be advised of the following warnings pertaining to contact lens wear:

EYE PROBLEMS, INCLUDING CORNEAL ULCERS, CAN DEVELOP RAPIDLY AND LEAD TO LOSS OF VISION; IF THE PATIENT EXPERIENCES:

- **Eye Discomfort,**
- **Excessive Tearing,**
- **Vision Changes,**
- **Loss of Vision,**
- **Eye Redness,**
- **Or Other Eye Problems,**

THE PATIENT SHOULD BE INSTRUCTED TO IMMEDIATELY REMOVE THE LENSES AND PROMPTLY CONTACT THE EYE CARE PROFESSIONAL.

- When prescribed for daily wear, patients should be instructed not to wear lenses while sleeping. Clinical studies have shown that the risk of serious adverse reactions is increased when lenses are worn overnight, and that the risk of ulcerative keratitis is greater for

extended wear contact lens users than for daily wear users.[3]

- Studies have shown that contact lens wearers who are smokers have a higher incidence of adverse reactions than nonsmokers.
- Problems with contact lenses or lens care products could result in serious injury to the eye. Patients should be cautioned that proper use and care of contact lenses and lens care products are essential for the safe use of these products.
- The overall risk of ulcerative keratitis may be reduced by carefully following directions for lens care.

[3] New England Journal of Medicine, September 21, 1989; 321 (12), pp. 773-783

Specific Instructions for Use and Warnings:

- **Water Activity**

  Instructions for Use

  Do not expose contact lenses to water while wearing them.

  WARNING:
  Water can harbor microorganisms that can lead to severe infection, vision loss or blindness. If lenses have been submersed in water when participating in water sports or swimming in pools, hot tubs, lakes, or oceans, the patient should be instructed to discard them and replace them with a new pair. The Eye Care Professional should be consulted for recommendations regarding wearing lenses during any activity involving water.

PRECAUTIONS

Special Precautions for Eye Care Professionals:

- Due to the small number of patients enrolled in clinical investigation of lenses, all refractive powers, design configurations, or lens parameters available in the lens material are not evaluated in significant numbers. Consequently, when selecting an appropriate lens design and parameters, the Eye Care Professional should consider all characteristics of the lens that can affect lens performance and ocular health, including oxygen permeability, wettability, central and peripheral thickness, and optic zone diameter.

- The potential impact of these factors on the patient's ocular health should be carefully weighed against the patient's need for refractive correction; therefore, the continuing ocular health of the patient and lens performance on the eye should be carefully monitored by the prescribing Eye Care Professional.
- Patients who wear these lenses to correct presbyopia using mono-vision may not achieve the best corrected visual acuity for either far or near vision. Visual requirements vary with the individual and should be considered when selecting the most appropriate type of lens for each patient.
- Fluorescein, a yellow dye, should not be used while the lenses are on the eyes. The lenses absorb this dye and become discolored. Whenever fluorescein is used in eyes, the eyes should be flushed with a sterile saline solution that is recommended for in-eye use.
- Eye Care Professionals should instruct the patient to remove the lenses immediately if the eyes become red or irritated.

Eye Care Professionals should carefully instruct patients about the following care regimen and safety precautions.

Handling Precautions:

- Before leaving the Eye Care Professional's office, the patient should be able to promptly remove the lenses or should have someone else available who can remove the lenses for him or her.
- DO NOT use if the sterile blister package is opened or damaged.
- Always wash and rinse hands before handling lenses. Do not get cosmetics, lotions, soaps, creams, deodorants, or sprays in the eyes or on the lenses. It is best to put on lenses before putting on makeup. Water-based cosmetics are less likely to damage lenses than oil-based products.
- DO NOT touch contact lenses with the fingers or hands if the hands are not free of foreign materials, as microscopic scratches of the lenses may occur, causing distorted vision and/or injury to the eye.
- Carefully follow the handling, insertion, removal, and wearing instructions in the "Patient Instruction Guide" for the prescribed

wearing schedule and those prescribed by the Eye Care Professional.

- Always handle lenses carefully and avoid dropping them.
- Never use tweezers or other tools to remove lenses from the lens container unless specifically indicated for that use. Slide the lens up the side of the bowl until it is free of the container.
- Do not touch the lens with fingernails.

Lens Wearing Precautions:

- If the lens sticks (stops moving) on the eye, follow the recommended directions in “Care for a Sticking (Non-Moving) Lens." The lens should move freely on the eye for the continued health of the eye. If non-movement of the lens continues, the patient should be instructed to immediately consult his or her Eye Care Professional.
- Never wear lenses beyond the period recommended by the Eye Care Professional.
- The patient should be advised to never allow anyone else to wear their lenses. They have been prescribed to fit their eyes and to correct their vision to the degree necessary. Sharing lenses greatly increases the chance of eye infections.
- If aerosol products, such as hair spray, are used while wearing lenses, exercise caution and keep eyes closed until the spray has settled.
- Avoid all harmful or irritating vapors and fumes while wearing lenses.
- Always discard lenses worn as prescribed by the Eye Care Professional.

Lens Care Precautions:

- The patient should be informed that no cleaning or disinfection is needed when lenses are worn for daily disposable wear. Patients should always dispose of lenses when removed and have spare lenses or spectacles available.

Other Topics to Discuss with Patients:

- Always contact the Eye Care Professional before using any medicine in the eyes.
- Certain medications, such as antihistamines, decongestants, diuretics, muscle relaxants, tranquilizers, and those for motion sickness may cause dryness of the eye, increased lens awareness, or blurred vision. Should such conditions exist, proper remedial measures should be prescribed. Depending on the severity, this could include the use of lubricating drops that are indicated for use with soft contact lenses or the temporary discontinuance of contact lens wear while such medication is being used.
- Oral contraceptive users could develop visual changes or changes in lens tolerance when using contact lenses. Patients should be cautioned accordingly.
- As with any contact lens, follow-up visits are necessary to assure the continuing health of the patient's eyes. The patient should be instructed as to a recommended follow-up schedule.

Who Should Know That the Patient is Wearing Contact Lenses?

- Patients should inform all doctors (Health Care Professionals) about being a contact lens wearer.
- Patients should always inform their employer of being a contact lens wearer. Some jobs may require use of eye protection equipment or may require that the patient not wear contact lenses.

ADVERSE REACTIONS

The patient should be informed that the following problems may occur when wearing contact lenses:

- The eye may burn, sting, and/or itch.
- There may be less comfort than when the lens was first placed on the eye.
- There may be a feeling of something in the eye (foreign body, scratched area).
- There may be the potential for some temporary impairment due to

peripheral infiltrates, peripheral corneal ulcers, or corneal erosion. There may be the potential for other physiological observations, such as local or generalized edema, corneal neovascularization, corneal staining, injection, tarsal abnormalities, iritis, and conjunctivitis; some of which are clinically acceptable in low amounts.

- There may be excessive watering, unusual eye secretions, or redness of the eye.
- Poor visual acuity, blurred vision, rainbows, or halos around objects, photophobia, or dry eyes may also occur if the lenses are worn continuously or for too long a time.

The patient should be instructed to conduct a simple 3-part self-examination at least once a day. They should ask themselves:

- How do the lenses feel on my eyes?
- How do my eyes look?
- Have I noticed a change in my vision?

If the patient reports any problems, he or she should be instructed to IMMEDIATELY REMOVE THE LENS. If the problem or discomfort stops, the patient should discard the lens and place a new fresh lens on the eye.

If after inserting the new lens, the problem continues, the patient should be directed to IMMEDIATELY REMOVE THE LENS AND CONTACT HIS OR HER EYE CARE PROFESSIONAL.

The patient should be instructed NOT to use a new lens as self-treatment for the problem.

The patient should be advised that when any of the above symptoms occur, a serious condition such as infection, corneal ulcer, neovascularization, or iritis may be present. He or she should be instructed to seek immediate professional identification of the problem and prompt treatment to avoid serious eye damage.

GENERAL FITTING GUIDELINES

A. Patient Selection
Patients selected to wear these lenses should be chosen based on:

- Motivation to wear lenses
- Ability to follow instructions regarding lens wear care
- General health
- Ability to adequately handle and care for the lenses
- Ability to understand the risk and benefits of lens wear

Patients who do not meet the above criteria should not be provided with contact lenses.

B. Pre-fitting Examination
Initial evaluation of the patient should begin with a thorough case history to determine if there are any contraindications to contact lens wear. During the case history, the patient's visual needs and expectations should be determined as well as an assessment of their overall ocular, physical, and mental health.
Preceding the initial selection of trial contact lenses, a comprehensive ocular evaluation should be performed that includes, but is not limited to, the measurement of distance and near visual acuity, distance and near refractive prescription (including determining the preferred reading distance for presbyopes), keratometry, and biomicroscopic evaluation.

Based on this evaluation, if it is determined that the patient is eligible to wear these lenses, the Eye Care Professional should proceed to the lens fitting instructions as outlined below.

C. Initial Power Determination

A spectacle refraction should be performed to establish the patient's baseline refractive status and to guide in the selection of the appropriate lens power. Remember to compensate for vertex distance if the refraction is greater than ±4.00D.

D. Base Curve Selection (Trial Lens Fitting)
The following trial lenses should be selected for patients regardless of keratometry readings. However, corneal curvature measurements should be performed to establish the patient's baseline ocular status.

- ACUVUE OASYS® 1-Day: 8.5 mm/14.3 mm
- ACUVUE OASYS® 1-Day for ASTIGMATISM: 8.5 mm/14.3 mm

The trial lens should be placed on each of the patient's eyes and evaluated after the patient has adjusted to the lenses.

1. Criteria of a Properly Fit Lens

   A properly fit lens will center and completely cover the cornea (i.e., no limbal exposure), have sufficient movement to provide tear exchange under the contact lens with the blink, and be comfortable. The lens should move freely when manipulated digitally with the lower lid, and then return to its properly centered position when released.

2. Criteria of a Flat Fitting Lens

   A flat fitting lens may exhibit one or more of the following characteristics: decentration, incomplete corneal coverage (i.e., limbal exposure), excessive movement with the blink, and/or edge standoff. If the lens is judged to be flat fitting, it should not be dispensed to the patient.

3. Criteria of a Steep Fitting Lens

   A steep fitting lens may exhibit one or more of the following characteristics: insufficient movement with the blink, conjunctival indentation, and resistance when pushing the lens up digitally with the lower lid. If the lens is judged to be steep fitting, it should not be dispensed to the patient.

If the initial trial base curve is judged to be flat or steep fitting, the alternate base curve, if available, should be trial fit and evaluated after the patient has adjusted to the lens. The lens should move freely when manipulated digitally with the lower lid, and then return to a properly centered position when released. If resistance is encountered when pushing the lens up, the lens is fitting tightly and should not be dispensed to the patient.

E. Final Lens Power (Spherical)

A spherical over-refraction should be performed to determine the final lens power after the lens fit is judged acceptable. The spherical over-refraction should be combined with the trial lens power to determine the final lens prescription. The patient should experience good visual acuity with the correct lens power unless there is [redacted]ve residual astigmatism.

Example 1	
Diagnostic lens:	-2.00D
Spherical over-refraction:	-0.25D
Final lens power:	-2.25D

Example 2	
Diagnostic lens:	-2.00D
Spherical over-refraction:	+0.25D
Final lens power:	-1.75D

If vision is acceptable, perform a slit lamp examination to assess adequate fit (centration and movement). If the fit is acceptable, dispense the lenses and instruct the patient to return in one week for reassessment (see dispensing and follow up information in **PATIENT MANAGEMENT**).

All patients should be supplied with a copy of the PATIENT INSTRUCTION GUIDE for these lenses. Copies are available for download at www.acuvue.com.

TORIC FITTING GUIDELINES

Although most aspects of the fitting procedure are identical for all types of soft contact lenses, including toric lenses, there are some additional steps and/or rules to follow to assure the proper fit of toric lenses.

The only new steps you must follow in prescribing ACUVUE OASYS® 1-Day for ASTIGMATISM are that you must determine the stability, repeatability, and drift angle of the lens axis so that you can prescribe the correct lens axis for the patient.

A. How to Determine Lens Cylinder and Axis Orientation

1. Locate the Orientation Marks

To help determine the proper orientation of the toric lens, you'll find two primary marks approximately 1 mm from the lens edge representing the vertical position on opposite ends of the lens at 6 and 12 o'clock (Fig. 1). Because of the lens' ballasting system, either mark can represent the vertical position – there is no "top" and "bottom" as in a prism-ballasted lens. You don't need to view both marks to assess orientation; simply look for the 6 o'clock mark as you would with a prism-ballasted lens.

Figure 1

You'll need a slit lamp biomicroscope with a 1 to 2 mm parallelepiped beam to highlight the marks when the lens is fitted to the eye. There are a number of techniques you can use to improve the visibility of the 6 o'clock mark. Using a parallelepiped beam and medium magnification (10x or 15x), slowly pan down the lens, looking just below the direct illumination at the retroilluminated area. Backlighting the mark this way should make it more visible. Sometimes manipulating the lower lid may be necessary to uncover the mark.

2. Observe Lens Rotation and Stability

Observe the position and stability of the "bottom" mark. It usually stabilizes at the 6 o'clock position. If it does, calculation of the lens power will be straightforward. The 6 o'clock position is not a "must"; however, the absolute requirement is that the axis position be stable and repeatable.

The mark may stabilize somewhat left or right (drift) of the vertical meridian and still enable you to fit a toric lens for that eye, as long as the lens always returns to the same "drift axis" position after settling. The deviation can be compensated for in the final prescription. Your objective is to ensure that whatever position the initial lens assumes near 6 o'clock, this position must be stable and repeatable. With full eye movement or heavy blink, you may see the marks swing away, but they must return quickly to the original stable position. If the lens does not return quickly, you may need to select a different lens.

3. Assessing Rotation

Imagine the eye as a clock dial and every hour represents a 30° interval. If the orientation mark of the initial lens stabilizes somewhat left or right of the vertical position, the final lens will orient on the eye with the same deviation. You can use an axis reticule in the slit lamp or use a line-scribed lens in a spectacle trial frame to measure or estimate the "drift angle" of the cylinder axis.

To compensate for this "drift", measure or estimate the "drift", then add or subtract it from the refractive axis to determine the correct cylinder axis. Use the LARS (Left Add, Right Subtract) method to determine which direction to compensate.

B. Final Lens Power

When the diagnostic lens has its axis aligned in the same meridian as the patient's refractive axis, a spherocylindrical over-refraction may be performed and visual acuity determined. However, in the case of crossed axes, such as when the diagnostic lens axis is different from the spectacle cylinder axis, it is not advisable to perform a full spherocylindrical over-refraction because of the difficulty in computing the resultant power. A spherical over-refraction without cylinder refraction may be performed.

If the required cylinder correction falls between two available cylinder powers, it is recommended to prescribe the lower cylinder power lens. See below for instructions on how to determine the final lens power.

1. For the Sphere

If sphere alone or combined sphere and cylinder Rx > ±4.00D, compensate for vertex distance. If sphere alone or combined sphere and cylinder Rx ≤ ±4.00D, vertex compensation is not necessary.

2. For the Cylinder

Adjust the axis by the drift angle using the LARS method. Choose a cylinder that is ≤ 0.50D from the refractive cylinder.

3. Case Examples

Example 1

Manifest (spectacle) refraction:
O.D. -2.50D / -1.25D x 180° 20/20
O.S. -2.00D / -1.00D x 180° 20/20

Choose a diagnostic lens for each eye with axis 180°. Place the lens on each eye and allow a minimum of 3 minutes for it to equilibrate, based on the patient's initial response to the lens. If the lens has not yet stabilized, recheck until stable.

Check the orientation of the axis mark. If the bottom axis mark is in the 6 o'clock position on both eyes, choose the appropriate cylinder as listed previously. If the lens has not yet stabilized, recheck until stable.

Here is the Rx Prescribed:
O.D. -2.50D / -1.25D x 180°
O.S. -2.00D / -0.75D x 180°

Example 2
Manifest (spectacle) refraction:
O.D. -3.00D / -1.00D x 90° 20/20
O.S. -4.75D / -2.00D x 90° 20/20

Choose diagnostic lenses of -3.00D / -0.75D x 90° for the right eye and -4.50D / -1.75D x 90° for the left eye, the nearest lenses available to the spherical power, cylinder power, and axis needed. For the left eye, since the manifest refraction called for -4.75D, compensating for vertex distance the sphere is reduced by 0.25D to -4.50D. The cylinder power will be -1.75D. Place the lens on each eye and allow a minimum of 3 minutes for it to equilibrate, based on the patient's initial response to the lens. If the lens has not yet stabilized, recheck until stable.

Right Eye

The orientation mark on the right lens rotates left from the 6 o'clock position by 10° and remains stable in this position. Compensation for this rotation should be done as follows:

Compensate the 10° axis drift by adding it to the manifest refraction axis.

Here is the Rx Prescribed:
O.D. -3.00D / -0.75D x 100°

Left Eye

The orientation mark on the left lens rotates right from the 6 o'clock position by 10° and remains stable in this position.

Compensate for the 10° axis drift by subtracting it from the manifest refraction axis.

Here is the Rx Prescribed:
O.S. -4.50D / -1.75D x 80°

If vision is acceptable, perform a slit lamp examination to assess adequate fit (centration and movement). If fit is acceptable, dispense the lenses instructing the patient to return in one week for reassessment (see dispensing and follow-up information in PATIENT MANAGEMENT).

All patients should be supplied with a copy of the PATIENT INSTRUCTION GUIDE for these lenses. Copies are available for download at www.acuvue.com.

MONOVISION FITTING GUIDELINES

A. Patient Selection

1. Monovision Needs Assessment

For a good prognosis, the patient should have adequately corrected distance and near visual acuity in each eye. The amblyopic patient or the patient with significant astigmatism (greater than 1.00D) in one eye may not be a good candidate for monovision correction with these lenses.

Occupational and environmental visual demands should be considered. If the patient requires critical vision (visual acuity and stereopsis), it should be determined by trial whether this patient can function adequately with monovision correction. Monovision contact lens wear may not be optimal for activities such as:

- visually demanding situations such as operating potentially dangerous machinery or performing other potentially hazardous activities; and
- driving automobiles (e.g., driving at night). Patients who cannot meet state driver's licensing requirements with monovision correction should be advised to not drive with this correction, OR may require that additional over-correction be prescribed.

2. Patient Education

All patients do not function equally well with monovision correction. Patients may not perform as well for certain tasks with this correction as they have with spectacles (multifocal, bifocal, trifocal, readers, progressives). Each patient should understand that monovision, as well as other presbyopic alternatives, can create a vision compromise that may reduce visual acuity and depth perception for distance and near tasks. Therefore, caution should be exercised when the patient is wearing the correction for the first time until they are familiar with the vision provided in visually challenging environments (e.g., reading a menu in a dim restaurant, driving at night in rainy/foggy conditions, etc.). During the fitting process, it is necessary for the patient to realize the disadvantages as well as the advantages of clear near vision and straight ahead and upward gaze that monovision contact lenses provide.

B. Eye Selection

1. Ocular Preference Determination Methods

Generally, the non-dominant eye is corrected for near vision. The following two methods for eye dominance can be used.

Method 1: Determine which eye is the “sighting eye.” Have the patient point to an object at the far end of the room. Cover one eye. If the patient is still pointing directly at the object, the eye being used is the dominant (sighting) eye.

Method 2: Determine which eye will accept the added power with the least reduction in vision. Place a hand-held trial lens equal to the spectacle near ADD in front of one eye and then the other while the distance refractive error correction is in place for both eyes. Determine whether the patient functions best with the near ADD lens over the right or left eye.

2. Other Eye Selection Methods

Other methods include the "Refractive Error Method" and the "Visual Demands Method."

Refractive Error Method

For anisometropic correction, it is generally best to fit the more hyperopic (less myopic) eye for distance and the more myopic (less hyperopic) eye for near.

Visual Demands Method

Consider the patient’s occupation during the eye selection process to determine the critical vision requirements. If a patient’s gaze for near tasks is usually in one direction, correct the eye on that side for near.

Example: A secretary who places copy to the left side of the desk will function best with the near lens on the left eye.

C. Special Fitting Characteristics

1. Unilateral Vision Correction

There are circumstances where only one contact lens is required. As an example, an emmetropic patient would only require a near lens, whereas a bilateral myope would require corrective lenses on

both eyes.

Examples:

A presbyopic emmetropic patient who requires a +1.75D ADD would have a +1.75D lens on the near eye and the other eye left without correction.

A presbyopic patient requiring a +1.50D ADD who is -2.50D myopic in the right eye and -1.50D myopic in the left eye may have the right eye corrected for distance and the left uncorrected for near.

2. Near ADD Determination

Always prescribe the lens power for the near eye that provides optimal near acuity at the midpoint of the patient's habitual reading distance. However, when more than one power provides optimal reading performance, prescribe the least plus (most minus) of the powers.

3. Trial Lens Fitting

A trial fitting is performed in the office to allow the patient to experience monovision correction. Lenses are fit according to the GENERAL FITTING GUIDELINES for base curve selection described in this Package Insert.

Case history and standard clinical evaluation procedure should be used to determine the prognosis. Determine the distance correction and the near correction. Next determine the near ADD. With trial lenses of the proper power in place, observe the reaction to this mode of correction.

Allow the lenses to settle for about 20 minutes with the correct power lenses in place. Walk across the room and have the patient look at you. Assess the patient's reaction to distance vision under these circumstances. Then have the patient look at familiar near objects such as a watch face or fingernails. Again assess the reaction. As the patient continues to look around the room at both near and distance objects, observe the reactions. Only after these vision tests are completed should the patient be asked to read print. Evaluate the patient's reaction to large print (e.g., typewritten copy) at first and then graduate to newsprint and finally smaller type sizes.

After the patient's performance under the above conditions is completed, tests of visual acuity and reading ability under

conditions of moderately dim illumination should be attempted.

An initial unfavorable response in the office, while indicative of a guarded prognosis, should not immediately rule out a more extensive trial under the usual conditions in which a patient functions.

4. Adaptation

Visually demanding situations should be avoided during the initial wearing period. A patient may at first experience some mild blurred vision, dizziness, headaches, and a feeling of slight imbalance. You should explain the adaptational symptoms to the patient. These symptoms may last for a brief minute or for several weeks. The longer these symptoms persist, the poorer the prognosis for successful adaptation.

To help in the adaptation process, the patient can be advised to first use the lenses in a comfortable familiar environment such as in the home.

Some patients feel that automobile driving performance may not be optimal during the adaptation process. This is particularly true when driving at night. Before driving a motor vehicle, it may be recommended that the patient be a passenger first to make sure that their vision is satisfactory for operating an automobile. During the first several weeks of wear (when adaptation is occurring), it may be advisable for the patient to only drive during optimal driving conditions. After adaptation and success with these activities, the patient should be able to drive under other conditions with caution.

D. Other Suggestions

The success of the monovision technique may be further improved by having the patient follow the suggestions below:

- Have a third contact lens (distance power) to use when critical distance viewing is needed.
- Have a third contact lens (near power) to use when critical near viewing is needed.
- Having supplemental spectacles to wear over the monovision contact lenses for specific visual tasks may improve the success of monovision correction. This is particularly applicable for those patients who cannot meet state driver's licensing requirements with monovision correction.
- Make use of proper illumination when carrying out visual tasks.

Monovision fitting success can be improved by the following suggestions:

- Reverse the distance and near eyes if a patient is having trouble adapting.
- Refine the lens powers if there is trouble with adaptation. Accurate lens power is critical for presbyopic patients.
- Emphasize the benefits of clear near vision and straight ahead and upward gaze with monovision.

The decision to fit a patient with monovision correction is most appropriately left to the Eye Care Professional in conjunction with the patient after carefully considering the patient's needs.

All patients should be supplied with a copy of the PATIENT INSTRUCTION GUIDE for these lenses. Copies are available for download at www.acuvue.com.

PATIENT MANAGEMENT

Dispensing Visit

Each sterile lens is supplied in a foil-sealed plastic package containing buffered saline solution with methyl ether cellulose. To remove the lens from the container, peel back the foil seal, place a finger on the lens, and slide the lens up the side of the bowl of the lens package until it is free of the container.

- Evaluate the physical fit and visual acuity of the lens on each eye.
- Teach the patient how to apply and remove his or her lenses.
- Explain daily disposable lens wear and schedule a follow-up examination.
- **Provide the patient with a copy of the PATIENT INSTRUCTION GUIDE for these lenses. Copies are available for download at www.acuvue.com.**

  REVIEW THESE INSTRUCTIONS WITH THE PATIENT SO THAT HE OR SHE CLEARLY UNDERSTANDS THE PRESCRIBED WEARING AND REPLACEMENT SCHEDULES.

Follow-Up Examinations

Follow-up care (necessary to ensure continued successful contact lens wear) should include routine periodic progress examinations, management of specific problems, if any, and a review with the patient of the wear schedule, daily disposable modality, and proper lens handling procedures.

Recommended Follow-up Examination Schedule (complications and specific problems should be managed on an individual patient basis):

1. One week from the initial lens dispensing to patient
2. One month post-dispensing
3. Every three to six months thereafter

NOTE: Preferably, at the follow-up visits, lenses should be worn for at least six hours.

Recommended Procedures for Follow-up Visits:

1. Solicit and record patient's symptoms, if any.
2. Measure visual acuity monocularly and binocularly at distance and near with the contact lenses.
3. Perform an over-refraction at distance and near to check for residual refractive error.
4. With the biomicroscope, judge the lens fitting characteristics (as described in the **GENERAL FITTING GUIDELINES**) and evaluate the lens surface for deposits and damage.
5. Following lens removal, examine the cornea and conjunctiva with the biomicroscope and fluorescein (unless contraindicated).
   - The presence of vertical corneal striae in the posterior central cornea and/or corneal neovascularization is indicative of excessive corneal edema.
   - The presence of corneal staining and/or limbal-conjunctival hyperemia can be indicative of an unclean lens, a reaction to solution preservatives, excessive lens wear and/or a poorly fitting lens.
   - Papillary conjunctival changes may be indicative of an unclean and/or damaged lens.
6. Periodically perform keratometry and spectacle refractions. The values should be recorded and compared to the baseline measurements.

If any observations are abnormal, use professional judgment to alleviate the problem and restore the eye to optimal conditions. If

the criteria for successful fit are not satisfied during any follow-up examinations, repeat the patient's trial fitting procedure and refit the patient.

WEARING SCHEDULE

The wearing schedule should be determined by the Eye Care Professional. Regular checkups, as determined by the Eye Care Professional, are also extremely important.

Patients tend to overwear the lenses initially. The Eye Care Professional should emphasize the importance of adhering to the initial maximum wearing schedule. Maximum wearing time should be determined by the Eye Care Professional based upon the patient's physiological eye condition, because individual response to contact lenses varies.

The maximum suggested wearing time for these lenses is:

Day	Hours
1	6-8
2	8-10
3	10-12
4	12-14
5 and after	all waking hours

REPLACEMENT SCHEDULE

These lenses are indicated for daily disposable wear and should be discarded upon removal.

LENS CARE DIRECTIONS

When lenses are prescribed for daily disposable wear, the Eye Care Professional should provide the patient with appropriate and adequate warnings and instructions for daily disposable lens wear at the time they are dispensed.

The Eye Care Professional should review with patients that no cleaning or disinfection is needed with daily disposable lenses. Patients should always dispose of lenses when they are removed and have spare lenses or spectacles available.

Basic Instructions

- Always wash, rinse, and dry hands before handling contact lenses.
- Do not use saliva or anything other than the recommended solutions for lubricating or rewetting lenses. Do not put lenses in the mouth.
- Eye Care Professionals may recommend a lubricating/rewetting solution which can be used to wet (lubricate) lenses while they are being worn to make them more comfortable.

Care for a Sticking (Non-Moving) Lens

If the lens sticks (stops moving), the patient should be instructed to apply a few drops of the recommended lubricating or rewetting solution directly to the eye and wait until the lens begins to move freely on the eye before removing it. If non-movement of the lens continues after a few minutes, the patient should immediately consult the Eye Care Professional.

EMERGENCIES

The patient should be informed that if chemicals of any kind (household products, gardening solutions, laboratory chemicals, etc.) are splashed into the eyes, the patient should: FLUSH EYES IMMEDIATELY WITH TAP WATER AND IMMEDIATELY CONTACT THE EYE CARE PROFESSIONAL OR VISIT A HOSPITAL EMERGENCY ROOM WITHOUT DELAY.

HOW SUPPLIED

Each UV-blocking sterile lens is supplied in a foil-sealed plastic package containing buffered saline solution with methyl ether cellulose. The plastic package is marked with the following:

- ACUVUE OASYS® 1-Day: base curve, power, diameter, lot number, and expiration date
- ACUVUE OASYS® 1-Day for ASTIGMATISM: base curve, power, diameter, cylinder, axis, lot number, and expiration date

REPORTING OF ADVERSE REACTIONS

All serious adverse experiences and adverse reactions observed in patients wearing these lenses or experienced with these lenses should be reported to:

Johnson & Johnson Vision Care, Inc.
7500 Centurion Parkway
Jacksonville, FL 32256
USA
Tel: 1-800-843-2020
www.acuvue.com

Johnson & Johnson Vision Care, Inc.
7500 Centurion Parkway
Jacksonville, FL 32256
USA
Tel: 1-800-843-2020
www.acuvue.com

20401080

In Canada: Johnson & Johnson Vision Care, division of Johnson & Johnson, Inc.
In USA: Johnson & Johnson Vision Care, Inc.
Printed in USA.
Revision date: 09/16
Revision number: AO-03-16-13

APPENDIX D: [redacted]

- [redacted], Subject Reported Ocular Symptoms/Problems
- [redacted], Patient Reported Outcomes

[redacted], SUBJECT REPORTED OCULAR SYMPTOMS/PROBLEMS

[redacted]

[redacted]

APPENDIX E: EUROLENS RESEARCH SOP #12A, THE SET UP, MEASUREMENT OF VISUAL ACUITY AND PROCEDURES FOR CARRYING OUT AN OVER REFRACTION USING THE EUROLENS COMPUTERISED LOGMAR VA CHART

Eurolens Research

Clinical
Standard Operating Procedure

The set up, measurement of visual acuity and procedures for carrying out an over refraction using the Eurolens computerised logMAR VA chart

Neil Chatterjee
Research Optometrist

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Director

Summary

This document contains details of:

1. Overview of chart design.
2. The procedure of calibration and set up of the Eurolens computerised logMAR chart.
3. A method of measurement of VA using the Eurolens chart.
4. A method of carrying out an over refraction for clinical study contact lenses when visual performance is being measured using the Eurolens chart at 6m.

Responsibilities

GOC-registered study investigators/research optometrists.

Definitions/Acronym

logMAR - logarithmic value of the minimum angle of resolution.

The MAR relates to the resolution required to resolve the elements of a letter. logMAR is the $\log_{10}$ of the MAR. (**Table 1**)

Snellen	Decimal	MAR	logMAR
6/60	0.10	10	1.00
6/24	0.25	4	0.602
6/12	0.50	2	0.301
6/6	1.00	1	0.000
6/4	1.50	0.667	-0.176

Table 1. The relationship between different acuity measurements

Optotype – A standardised symbol for testing vision.

Over refraction – the amount, in Dioptres (D), that will be accepted by a subject over a contact lens in order to obtain the optimum visual performance when viewing a visual acuity test chart.

Chart design

1. The Eurolens computerised logMAR visual acuity chart (hereafter referred to as Eurolens chart) is a logMAR chart designed to run on an Apple Macintosh with

Microsoft Excel software. The chart is displayed through an external monitor connected to the Apple Mac via its monitor socket and appropriate cable.

2. The Eurolens chart is similar in design to the traditional Bailey-Lovie logMAR chart, however it uses a reversed Sloan font as the optotype. The need for the reversed font is due to the chart being viewed indirectly in a mirror in a 3m consulting room. The chart is mounted on an adjustable mount, above the subject's head.
3. The indirect viewing makes the effective distance of the chart 6m from the subject. This 6m distance is the standard testing distance in optometric practice.
4. High (100%) and low (10%) contrast VA measurements can be taken with the chart.
5. The VA measurement from the Eurolens chart is intended to be equivalent to that obtained from the traditional Bailey-Lovie logMAR charts at 6m. The Eurolens chart has two advantages over the Bailey-Lovie. The Eurolens chart does not fade or discolour (which reduces legibility). Further, unlike the fixed Bailey-Lovie chart, the letters can be randomised on the Eurolens chart, which reduces the effect of memory influencing the subject's VA score.

Initial computer set up

1. The Apple Macintosh should have the following installed:
    a. Reversed Sloan font (otf file, which should be copied to the Macintosh HD/Library/Fonts/ folder)
    b. Microsoft Office 2011 or later
    c. Eurolens chart v5 software
2. The external monitor should be connected to the Mac. It will require the use of an appropriate adaptor and cable.
3. The additional monitor should be recognised automatically by the Mac. The Mac should configure the monitor as a second desktop. To verify this, move the mouse pointer across the screen. It should be possible to move the mouse pointer off the edge of the main screen and it should appear on the external monitor.
4. The Eurolens Chart software is an Excel file called Eurolens Research chart.xls. This, for convenience, is located on the desktop.
5. To run the chart, open the Excel file. Click on "enable macros".
6. The chart should be displayed on the external monitor and the chart's control panel should appear on the Mac's main screen (**Figure 1**).

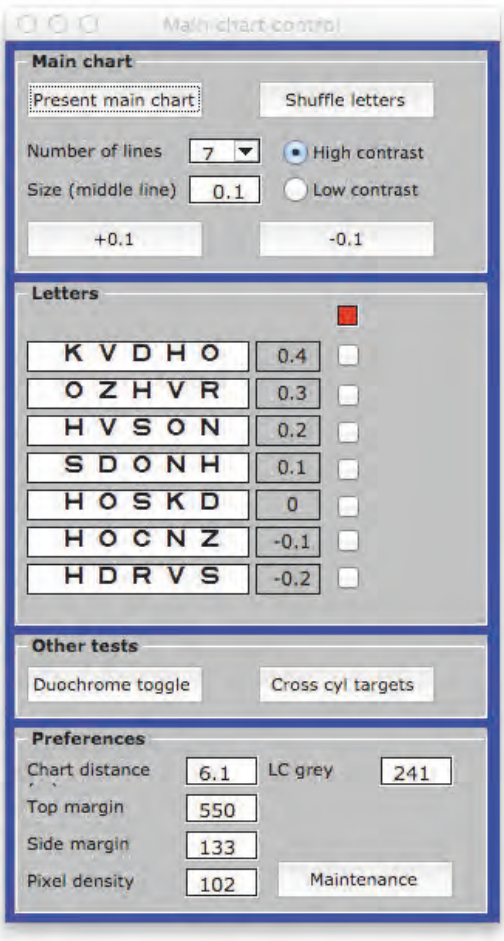


Figure 1. Chart control panel

7. If the letter chart appears on the Mac's main screen, it will need to be "dragged" onto the external monitor. To do this the chart control box must be closed. The main chart can now be dragged onto the second screen and maximised.
8. To restart the control panel, click on the Excel icon in the dock. Then in Excel's menu, select.: Tools -> Macro-> Macros. A macro box should appear, select the macro entitled 'showform' and click on run. The chart's control panel can be reopened if closed (e.g. accidentally) by repeating this step.

Chart calibration procedure

1. It is important the charts are calibrated before first use, to ensure the optotypes are of the correct size and contrast. Minute adjustments of monitor contrast or brightness can affect the contrast of the letters (especially low).

2. If the chart distance is set to 6m, the 0.8 letter on the computer chart should be the same height as that on the Bailey-Lovie chart, measuring just under 55mm high.
3. The chart distance should then be set to the distance of the subject's head to the chart.
4. The monitor should be inclined downwards at an angle of approximately five degrees from the vertical. The reason being the contrast of an LCD monitor can vary with tilt. At five degrees of inclination, the monitor will be 'straight on' for the subject sat on the chair below. (see Appendix A)
5. The monitor should then be calibrated using a Datacolor Spyder 4. Whilst calibrating, the room lights should be on full illumination and the monitor set to factory default values (all setting "standard"). The corresponding monitor profile file generated should be saved and then used as the profile for the external monitor.
6. The contrast of the low contrast chart should be measured. The test spreadsheet (low contrast grey test.xlsx) should be displayed on the monitor with room lights on. Measurements of the luminance of the grey and white halves are taken with the spyder. The luminance measurements are then averaged. The contrast of the grey to white backgrounds is calculated as follows:

$$\% \text{ contrast} = \frac{\text{white lum} - \text{grey lum}}{\text{white lum}} \times 100$$

7. The RGB vales of the grey background should be altered until the contrast is calculated to be approximately 10%. This value is usually between 240 and 245 units.
8. Acuity measurements on the freshly calibrated chart should then be compared to those taken with two already calibrated charts. This is done by measuring high and low contrast visual acuity with all three charts (in a randomised order on around eight subjects). The acuity measurements of the three charts should all agree within two letters (0.04 logMAR) for high and low contrast acuity.
9. If the high contrast acuity on the test chart does not agree with that of the control charts, then the "chart distance" value should be altered on the test chart, until it is in agreement with the controls.
10. Once the high contrast acuity values are in agreement, the test chart's low contrast acuity should be in agreement with the control. If not then the "LC grey" value should be altered on the test chart until agreement is reached.

11. Final settings for each monitor on 11 October 2017 are contained in Appendix B.

Measurement of VA using the Eurolens chart

General instructions

1. The subject should be seated in the chair 3m from the mirror. This will place the chart at a 6m testing distance.
2. The default test chart for standard testing should be a 7-line chart ranging from 0.4 to -0.2 (Figure 1).
3. The subject's acuity can be tested monocularly and/or binocularly according to the study protocol.
4. If the subject cannot read the top line then increase letter size in 0.1 steps until the subject can see the top line.
5. Adjusting the "number of lines" box can alter the number of rows of letters displayed on the chart. Please note to display larger letters (over 0.4), then only one or three rows should be selected.
6. Letters can be increased in size by 0.1 steps, by clicking on the "+0.1" box. Letters can be increased in size to a maximum of 1.0.
7. Letters can be decreased in size by clicking on "-0.1".
8. The control panel displays information on the optotypes currently displayed on the chart and their size in logMAR.
9. The VA score is calculated using the same method as a traditional Bailey-Lovie chart, with each letter scoring 0.02 units and each complete line scoring 0.1 (see below).
10. To display the high contrast chart select "high contrast", similarly to display the low contrast chart select "low contrast". This will display letters of 100% and 10% contrast respectively
11. The Mac generates the sequence of letters used in the chart randomly. Clicking on "shuffle letters" can change the sequence of letters.
12. Letters should be shuffled after each VA measurement to avoid the subject learning the chart.
13. As the chart is at 6m, any over-refraction performed can be considered to be equivalent to that performed on a 6m Snellen chart i.e. at infinity.

14. The 6m testing distance should also be taken into account when comparing logMAR scores obtained with the Bailey-Lovie chart at 3m. The Bailey-Lovie scores should differ by -0.3.

Subject instructions (standard chart display)

After positioning the subject at the desired test distance, initiate the testing as follows:

1. Ask the subject to read the smallest line where they feel they can easily read all the letters. If the subject reads all the letters on the initial line, encourage them to continue reading the smaller lines until three or more letters on a 5- letter line are incorrectly identified.
2. If the subject identifies one letter incorrectly on the initial line, ask them to read the line(s) above until one complete line has been identified correctly. Then encourage the subject to continue reading the smaller lines/letters until three or more letters on a 5-letter line are incorrectly identified. *Note: The subject is to be encouraged to read and even guess at the letters until three or more letters are incorrectly identified.*

Scoring

To determine the VA unit score for a given line: Take the maximum VA for the last line read (i.e. the line on which three or more letters were missed) and add +0.02 for every letter missed on the chart.

For example:

i)	0.00 line	3 letters missed	logMAR score +0.06
ii)	+0.20 line	0 letters missed	
	+0.10 line	2 letters missed	
	0.00 line	3 letters missed	logMAR score +0.10
iii)	-0.20 line	0 letters missed	
	-0.30 line	2 letter missed	
	-0.40 line	4 letters missed	logMAR score –0.28

Over-refraction

Unless the clinical study protocol states otherwise the following procedures should be carried out:

1. Visual acuity using the Eurolens chart will be measured with no over-refraction in place. The study protocol may require that this be carried out monocularly or binocularly.
2. A binocular over-refraction should be carried out using the chart at 6m. This procedure will control accommodation and allow accurate assessment of the subject's visual status. These results will allow the Investigator to judge whether or not the contact lens BVP is acceptable.

Bailey Lovie chart

LogMAR visual acuity can also be measured on a card-based Bailey-Lovie chart. The use of this chart is covered in more detail in the relevant SOP[1]. In summary the differences are:

1. Unless specified the Bailey-Lovie chart is used at a testing distance of 3m as it is viewed directly.
2. The font used (5x5 sans-serif font)[2] is that defined in the British Standard: BS 4274.
3. If the Bailey-Lovie is used at 3m, then it should not be used as a target to determine over-refraction. Instead an alternative chart (e.g. Snellen) positioned at 6m should be used.

References

1. Eurolens Research Standard Operating Procedure. Assessment of visual performance using the Bailey-Lovie logMAR visual acuity test chart and procedures for carrying out an over-refraction.
2. BS 4274-1:2003. Visual acuity test types. Test charts for clinical determination of distance visual acuity – Specification.

Appendix A. Screen inclination calculation

To calculate chart inclination

$$\text{Tan (angle of chart inclination)} = \frac{\text{Subject's distance below chart}}{\text{Subject to chart distance (parallel to floor)}}$$

Room	1.015	1.014	1.013	1.012
Subject's distance below chart (eye to top of monitor) (cm)*	50	65	65	65
Subject to chart distance (parallel to floor) (cm)	600	605	610	600
Calculated chart inclination (degrees)	4.7	6.1	6.1	6.2

Table 2: Eurolens clinic room screen inclination.

* Subject with Eurolens ID 2023 of average UK male height (175cm, ONS data) was used

Appendix B. Example of chart settings (11 October 2017)

Clinic room	1.012	1.013	1.014	1.015	1.018
Monitor number	4	5	3	1	2
Chart distance (m)	6.0	6.1	6.05	6.0	6.1
LC grey	240	240	243	240	237

Table 3: Eurolens clinic room chart settings

All monitors calibrated were a BenQ G2255 displaying the chart at native resolution (1920x1080).

Appendix C. Revisions to chart software

2008

Initial clinic version of computer chart software

01/02/2013 v5

2013 version of chart software was rewritten for compatibility with Office 2011 and Mac OSX10.8. Contains the following amendments:

- Colours of the control box have been altered for better legibility with office 2011
- Chart letter display was updated for 16:9 monitors
- Letter size is calculated correctly for chart distance
- Low contrast letters contrast adjustable from chart control panel.

APPENDIX F: EUROLENS RESEARCH SOP #16, MEDMONT E300 (TOPOGRAPHY AND TEAR FILM ANALYSIS)

Eurolens Research

Clinical
Standard Operating Procedure

Medmont E300
(topography and tear film analysis)

Sarah Smith
Research Optometrist

First issued: v0; July 30, 2002
Reviewed (with changes): v1; January 23, 2004
Reviewed (with changes): v2; May 4, 2012
Reviewed (with changes): v3; March 28, 2014
Reviewed (no changes): v3; April 15, 2016
Reviewed (no changes): v3; July 3, 2018
Reviewed (with changes): v4; October 25, 2018

Document control

Title:	Medmont E300 (topography and tear film analysis)
Document type:	Clinical standard operating procedure
Number of pages:	4

Document author: _____ Date: 25 Oct 2018
Sarah Smith
Research Optometrist

Document reviewed and approved by: _____ Date: 25 Oct 2018
Michelle Inwood
Project Officer (Business Systems)

Document approved by: _____ Date: 25-Oct-2018
Philip Morgan
Director

Summary

This document describes the procedures when using the Medmont E300 to obtain non-invasive ocular measurements including:

- Topography
- Tear film analysis

Responsibilities

Clinical investigators or trained personnel would normally carry out these non-invasive procedures.

Equipment Required

- Medmont E300 (Medmont International Pty Ltd Victoria, Australia)
- Medmont Studio software (v6.2.3 or above)
- Calibration object
- Antimicrobial disposable wipes to sanitise the headrest and chinrest
- Medmont manual

Procedures

Performing Examinations

1. Search or add subject details using Medmont studio software.
2. Confirm subject details before starting examination.
3. Position the subject correctly.
4. Select exam type (topography or tear film analysis).
5. Detailed guidance on the action required is provided on screen.

Notes:

Topography images are graded out of 100 based on centring, focusing and eye movement. A good score for a normal eye is over 75, and images should exceed this when being saved.

Full details can be found on pages 22-37 of v2.7 manual.

Back up of data

1. Data for all examinations are stored on the computer's hard drive in the directory: C:\Program Data\Medmont\Medmont Studio 6\Data.
2. To ensure these data are protected against hard drive failure, the computer's hard drive (including this directory) is automatically backed up to an external hard drive once a week using the Window 7 back-up wizard which is built into the computer's Windows XP operating system.
3. The Medmont software does have it's own backup facility (refer to Medmont Administrator Tool). This process is initiated manually and may be done on an ad-hoc basis.

Calibration

It is recommended to calibrate the E300 after installation or moving. The E300 will be calibrated annually where practicable. The calibration object itself should be verified and re-calibrated every two years.

1. Navigate to Configure > E300 > Instrument Setup.
2. From the E300 Instrument window, click on the installed instrument and click Calibrate to run the Calibration Wizard, which allows you to check the current calibration and optionally recalibrate the instrument.
3. Follow the on screen instructions.

Full details regarding calibration can be found on pages 80-84 of v2.7 manual.

References

Medmont E300 user manual v2.7 Sep 2015
https://www.medmont.com/files/ms6/manuals/E300.pdf

APPENDIX G: EUROLENS RESEARCH SOP #13, EXAMINATION OF THE ANTERIOR SEGMENT USING SLIT LAMP BIOMICROSCOPY

Eurolens Research

Clinical
Standard Operating Procedure

Examination of the anterior segment using slit lamp biomicroscopy

Carole Maldonado-Codina
Associate Director

First issued: v0; May 20, 2002
Reviewed (with changes): v2; June 26, 2009
Reviewed (no changes): v2; October 14, 2011
Reviewed (with changes): v3; March 4, 2014
Reviewed (with changes): v4; February 2, 2016
Reviewed (no changes): v4; February 5, 2018

Document control

Title:	Examination of the anterior segment using slit lamp biomicroscopy
Document type:	Clinical standard operating procedure
Number of pages:	4

Document author: Carole M-Codina Date: 2 Feb, 2016
Carole Maldonado-Codina
Associate Director

Document reviewed by: G Howarth Date: 2 feb 2016
Gillian Howarth
Research Optometrist

Document reviewed and approved by: Michelle Inwood Date: 2 Feb 2016
Michelle Inwood
Project Officer (Business Systems)

Document approved by: P Morgan Date: 2 Feb 2016
Philip Morgan
Director

Summary

The slit lamp biomicroscope is a high quality illuminating observation system which allows the external and internal ocular structures to be assessed in detail. The Efron Grading Scales for Contact Lens Complications[1] will be used to quantify most of the observations made. If an alternative grading scale is to be used this will be detailed in the study protocol.

Definitions

External ocular structures in this procedure refer to the following structures: conjunctiva, sclera, limbus and associated blood vessels, cornea, lids, lashes and tear film.

Internal ocular structures in this procedure refer to the anterior chamber.

Wratten 12 filter – A yellow filter which enhances the contrast of fluorescein staining when viewed using cobalt blue light.

Procedure

1. Using the recommended settings for slit width, magnification and filter, examine the external and internal ocular structures[2]. The following primary signs should be graded using the Efron Grading Scales: conjunctival redness, limbal redness, corneal neovascularisation, epithelial microcysts, corneal oedema and corneal infiltrates. The following secondary signs are also usually graded using the Efron Grading Scales: blepharitis and meibomian gland dysfunction. The number of mucin balls present are counted and recorded.
2. Instil sodium fluorescein (using a fluorescein ophthalmic strip wetted with saline) in both eyes and using cobalt blue light and a Wratten 12 filter or similar yellow filter, examine and grade the following: corneal and conjunctival staining. The location and 'type' of any staining is also usually recorded. Corneal staining type is usually divided into the following categories: no staining, toxicity, SEAL, foreign body/abrasion, inferior dehydration and non-specific.
3. The upper eyelid should then be everted and examined both with cobalt blue light (with the yellow filter in place) and with white light (no filter in place). The grading of upper palpebral conjunctivitis should then be made with the Efron Grading Scales.
4. If a soft contact lens needs to be applied after the examination, irrigate the eye with unpreserved sterile saline once the examination has been completed in order to remove excess sodium fluorescein.

Recording slit lamp findings

Grades for the appearance of the ocular structures are recorded and classified according to Table 1 using Efron Grading Scales. Grades are scored to the nearest 0.1 in the best judgment of the investigator, with the exception of mucin balls where the number is counted. Location of staining is categorised as either superior, inferior, central, nasal or temporal.

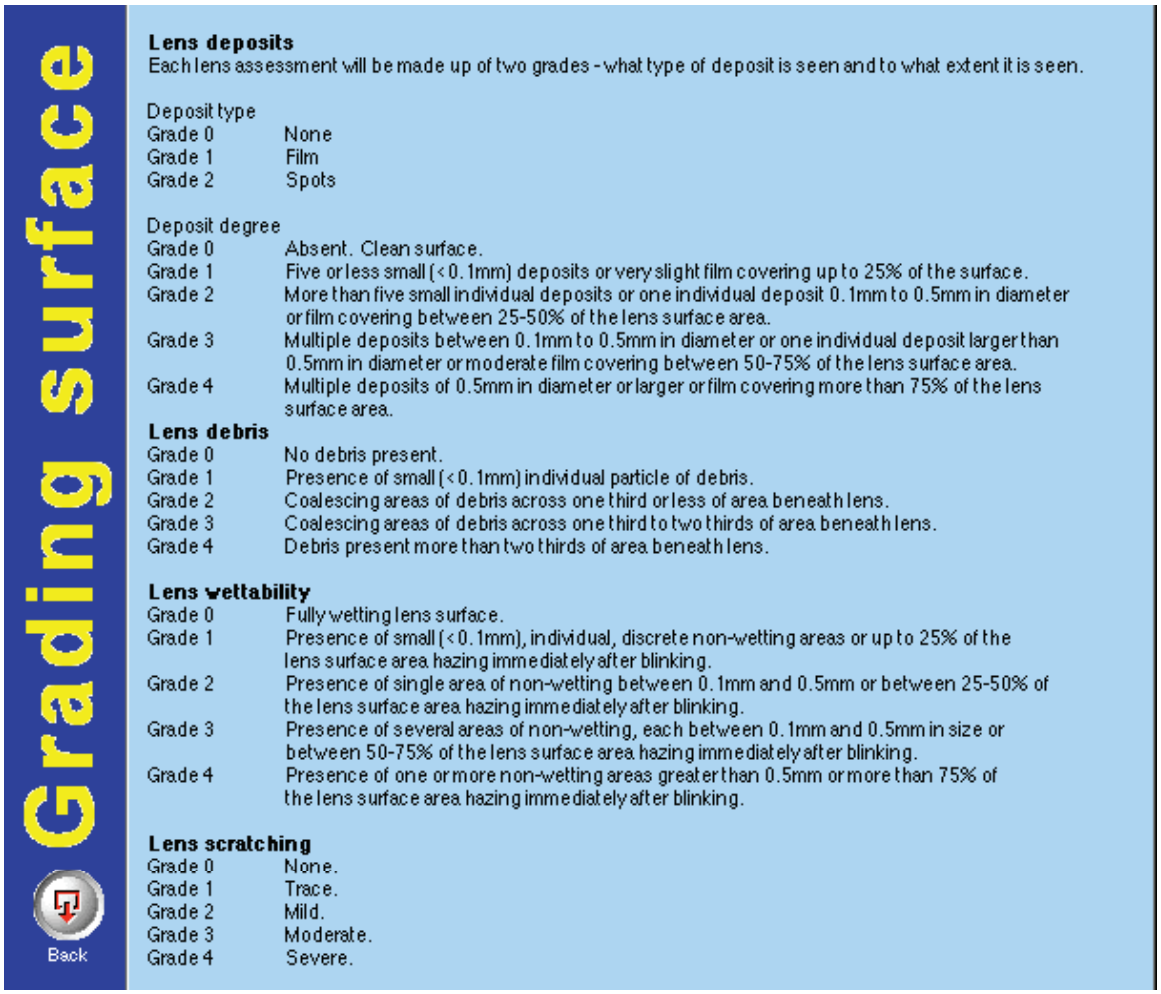
Classification	Primary signs	Secondary signs
Signs	Conjunctival redness Limbal redness Corneal neovascularisation Epithelial microcysts Corneal oedema Corneal infiltrates Corneal staining Location of staining Conjunctival staining Papillary conjunctivitis	Blepharitis Meibomian gland dysfunction Mucin balls
Scale	Efron Grading Scales (scored to nearest 0.1)	Efron Grading Scales (scored to nearest 0.1) (except mucin balls, where the number is recorded).

Table 1: Biomicroscopic signs.

References

1. Efron Grading Scales for Contact Lens Complications devised by Nathan Efron (2000 Millennium edition).
2. Morris J (2013). Slit lamp biomicroscopy. Optometry in Practice: 14 (3): 85-96.

APPENDIX H: EUROLENS RESEARCH GRADING SCALE (LENS FIT AND SURFACE ASSESSMENT)



Lens deposits
Each lens assessment will be made up of two grades - what type of deposit is seen and to what extent it is seen.

Deposit type

Grade 0	None
Grade 1	Film
Grade 2	Spots

Deposit degree

Grade 0	Absent. Clean surface.
Grade 1	Five or less small (< 0.1mm) deposits or very slight film covering up to 25% of the surface.
Grade 2	More than five small individual deposits or one individual deposit 0.1mm to 0.5mm in diameter or film covering between 25-50% of the lens surface area.
Grade 3	Multiple deposits between 0.1mm to 0.5mm in diameter or one individual deposit larger than 0.5mm in diameter or moderate film covering between 50-75% of the lens surface area.
Grade 4	Multiple deposits of 0.5mm in diameter or larger or film covering more than 75% of the lens surface area.

Lens debris

Grade 0	No debris present.
Grade 1	Presence of small (< 0.1mm) individual particle of debris.
Grade 2	Coalescing areas of debris across one third or less of area beneath lens.
Grade 3	Coalescing areas of debris across one third to two thirds of area beneath lens.
Grade 4	Debris present more than two thirds of area beneath lens.

Lens wettability

Grade 0	Fully wetting lens surface.
Grade 1	Presence of small (< 0.1mm), individual, discrete non-wetting areas or up to 25% of the lens surface area hazing immediately after blinking.
Grade 2	Presence of single area of non-wetting between 0.1mm and 0.5mm or between 25-50% of the lens surface area hazing immediately after blinking.
Grade 3	Presence of several areas of non-wetting, each between 0.1mm and 0.5mm in size or between 50-75% of the lens surface area hazing immediately after blinking.
Grade 4	Presence of one or more non-wetting areas greater than 0.5mm or more than 75% of the lens surface area hazing immediately after blinking.

Lens scratching

Grade 0	None.
Grade 1	Trace.
Grade 2	Mild.
Grade 3	Moderate.
Grade 4	Severe.

APPENDIX I: EUROLENS RESEARCH SOP #53, IN-VIVO CONFOCAL MICROSCOPY

Eurolens Research

Clinical
Standard Operating Procedure

In-vivo Confocal Microscopy

Neil Chatterjee
Research Optometrist

First issued: v1; January 16, 2017
Reviewed (with changes): v2; March 1, 2018

Document control

Title:	In-vivo Confocal Microscopy
Document type:	Clinical standard operating procedure
Number of pages:	8

Document author: _____ Date: 1 March 2018

Neil Chatterjee

Research Optometrist

Document reviewed and approved by: _____ Date: 1 Mar 2018.

Michelle Inwood

Project officer (Business Systems)

Document approved by: _____ Date: 02-March-2018

Philip Morgan

Director

Summary

In-vivo confocal microscopy is a non-invasive technique that visualises living tissue under high magnification, in healthy and pathological states. For the cornea, this instrument is able to capture cellular thickness of 1.3 to 2.1 μm; thus individual corneal layers can be examined.

The laser scanning confocal microcope described in this SOP is the Heidelberg Retina Tomograph III (HRT III) with the Rostock Corneal Module (RCM) attached.

Responsibilities

All users of the instrument, usually clinical investigators.

Definitions/Acronyms

- Viscotears (0.2% carbomer 980; Novartis UK) will be used as a coupling agent between the microscope and the TomoCap.
- Oxybuprocaine (minims 0.4% benoxinate hydrochloride) may be used to numb the eye during the examination.
- TomoCap (disposable Perspex applanating cap)
- HRT III - Heidelberg Retina Tomograph III
- RCM – Rostock Corneal module. This sits on the front of the HRT III and enables it to function as a confocal microscope.
- CCD – charge-coupled device
- HEYEX - Heidelberg Eye Explorer
- fps - frames per second
- FOV – field of view

Procedure

Preparation of the Camera

1. Power on the laptop and the HRT III.
2. The refraction of the HRT III's scanning camera (inside it's objective tube) should be set to to +12 dioptres.
3. Attach the RCM to the front of the HRT III's objective tube.
4. Move the RCM lens posteriorly by rotating the RCM wheel anticlockwise.

5. Apply a large homogenous, bubble-free amount of the ocular gel (Viscotears) on the RCM lens tip.
6. Remove a Tomocap from its sterile container and mount it over the lens tip. Be careful not to touch the front surface of the Tomocap at all time.

Creat subject file

1. Double click on the Heidelberg Eye Explorer (HEYEX) icon  .
2. Insert subject data and click OK.
3. The “Examination Data” dialog box is now displayed.
   a. In the “Device” field, select the device type in the drop-down list.
   b. In the “Operator” field, enter the operator’s name or select an existing entry from the drop-down list.
   c. In the “Study” field, enter a study or select an existing entry from the drop-down list.
4. In the “Diagnosis” tab, enter the subject diagnosis.
5. Click OK to confirm. “Corneal Module Settings” should now be displayed.
6. In the “Field Lens” field, select the appropiate field lens from the drop-down list.
7. Then click OK to confirm. The acquisition window should appear.

Camera adjustment and scan depth calibration

1. The acquisition window will display two live camera feeds. The confocal camera is displayed on the left and charge-coupled device (CCD) camera on the right.
2. Prior to acquiring confocal images, the focal plane of the instrument should be set to the anterior surface of the TomoCap.
3. Move the RCM lens anteriorly (by rotating the RCM collar clockwise) until the first bright image appears. This image represents the inner surface of the TomoCap.
4. Continue rotating the RCM collar until the second bright image appears. The depth value shown in the focus position display should now be between -150 µm and +150 µm. This second bright image represents the outer surface of the TomoCap.
5. Then reset the depth to 0 by clicking on the “Reset” button.

Subject preparation

1. Depending on the structure to be examined, it may be necessary to instil anaesthetic (Oxybuprocaine) and ocular gel (Viscotears) to the subject’s eye, to aid comfort.

2. Clean the chin rest and forehead bar using a wet disinfecting tissue.
3. The subject should be seated comfortably, with the chin on the chin rest and forehead resting firmly against the forehead bar.

Examining the subject

A) Cornea

1. Anaesthetic and ocular gel should be instilled into the subject's eye for corneal examination.
2. The subject should be instructed to fixate the HRT III's outer fixation light with the eye not being examined.
3. The CCD camera should be positioned perpendicular to the optical axis of the laser scanning camera.
4. The camera should be on the subject's right side when imaging the right eye and vice versa.
5. At this point, the investigator should see the front surface of the TomoCap in the centre of the CCD camera live image.
6. The mode of acquisition should be selected according to research/study purposes. The are three acquisition modes available for this instrument:
    a. *Section*: One single image is acquired and stored each time the foot switch is depressed.
    b. *Sequence*: A sequence of up to 100 images is acquired with an adjustable frame rate. A frame rate between 30 frames and 1 frame per second (fps) can be chosen and a movie with a duration of 3 to 100 seconds can be acquired.
    c. *Volume*: A series of 40 images is taken at consecutive focal planes. A total depth of 85 µm can be scanned with the "FOV 300 µm" and "FOV 400 µm" field lens. The focal distance between two consecutive images will be approximately 1.3 µm and 2.1 µm respectively.
7. Move the TomoCap towards the subject's cornea until it is approximately 5 to 10 mm away.
8. The RCM can be moved up/down or left/right using the black knobs on the HRT table. These should be adjusted until the TomoCap is in-line with the centre of the subject's cornea.

9. The subject's cornea and reflection of the red laser beam can be observed on the CCD camera window. Once the TomoCap is correctly aligned, the laser reflection should be in the centre of the cornea. If not, fine adjustments can be performed.
10. The subject should be instructed to open his/her eye as wide as possible. The RCM should be slowly moved forwards, until the Tomocap is in minimal contact with the subject's cornea.
11. Live confocal images of the cornea should now be observed. The foot pedal can be used to capture the live images.
12. If repositioning of the RCM is required, the TomoCap should be first moved away from the subject's cornea, the RCM repositioned, then the TomoCap can be replaced on the subject's cornea, and confocal imaging resumed.
13. When examining the cornea, it is important to not exert too much pressure on the subject's cornea, only a light touch is required. If too much pressure is placed on the cornea by the TomoCap, lines will appear in the live confocal image. If this occurs the TomoCap should be moved slightly backwards, to reduce pressure on the cornea (Tavakoli and Malik, 2011).

B) Bulbar conjunctiva

1. Anaesthetic and ocular gel should be instilled into the subject's eye for bulbar conjunctival examination.
2. The subject should be instructed to direct their gaze to the extreme opposite direction of the bulbar region to be scanned. For example, if the temporal bulbar conjunctiva of the right eye is to be scanned, the subject should be instructed to direct their gaze extremely to the left.
3. The subject should be asked to not change their fixation (where possible) throughout the examination.
4. An appropriate acquisition mode should be selected (explained in the *Cornea* section)
5. Move the RCM forward until the TomoCap is just in contact with the bulbar conjunctiva, and start scanning.
6. The foot pedal can be used to capture images during scanning.

C) Lid wiper and Palperbral conjunctiva

1. Both upper and lower lid wipers and nearby palpebal conjunctiva can be scanned with the RCM. No anaesthetic or ocular gel are required for this.
2. To examine the upper lid, the subject should be instructed to lower their gaze. The upper lid can then be everted with a cotton bud, and the lid margin taped against the subject's brow with surgical tape. Multiple pieces of tape may be required.
3. To examine the lower lid, the subject should be instructed to direct their gaze upwards, and the examiner's thumb used to gently to evert the lower lid. This should expose the lower lid wiper area.
4. The subject should be instructed to not change fixation throughout the examination.
5. The acquisition mode of the scan can now be selected (explained in the *Cornea* section)
6. Move the RCM module forward until The TomoCap is just in contact with the lid wiper area, and start scanning.
7. Use the foot pedal to capture images during the scan.

Post-examination procedures

1. After the examination is complete, turn the camera off by clicking the camera power button in the acquisition window.
2. If anaesthetic was used, the subject should be instructed to not rub their eyes until the local anesthesia has worn off. As a precaution, you may wish to perform a slit lamp examination of the subject's cornea after the examination.
3. The TomoCap should be changed between subjects and/or ocular surface examined (cornea, bulbar and lid wiper area) to avoid cross infection.
4. Remove the TomoCap from the RCM and dispose of it in the bio bin and then clean the RCM lens with a dry tissue.

Cleaning of confocal lens

Dried viscotears may crystalise and accumulate inside the RCM in-between the RCM lens at the metal collar. To prevent the build up of dried viscotears affecting operation of the instrument, the confocal lens and collar should be cleaned as required.

1. To perform the cleaning process the RCM must be part-dismantled and the metal collar and RCM lens removed. A specific spanner for this disassembly is kept in the wooden box with the spare RCM field lens.

2. The spanner is used to loosen the metal collar, it can then be uscrewed by hand. The RCM lens can then be untightened and removed by hand.
3. Using a moist tissue, any crystalised viscotears can be wiped off the side of the RCM lens. The inside of the metal collar can also be cleaned by this method.
4. Once dry the RCM can be reassambled. The sequence of reassembly is the reverse of disassembly.

References

TAVAKOLI, M. & MALIK, R. A. 2011. Corneal confocal microscopy: a novel non-invasive technique to quantify small fibre pathology in peripheral neuropathies. *J Vis Exp*.

APPENDIX J: EUROLENS RESEARCH SOP #58, MEASURING TEAR MENISCUS HEIGHT AND CROSS-SECTIONAL AREA USING OPTICAL COHERENCE TOMOGRAPHY

Eurolens Research

Clinical
Standard Operating Procedure

Measuring tear meniscus height and cross-sectional area using Optical Coherence Tomography

Research Associate
Maria Navascues-Cornago

First issued: v0; May 24, 2016
Reviewed (with changes): v1; September 9, 2016
Reviewed (with changes): v1.1; August 30, 2018

Document control

Title:	Measuring tear meniscus height and cross-sectional area using Optical Coherence Tomography
Document type:	Clinical standard operating procedure
Number of pages:	6

Document author: Maria Navascues-Cornago Date: 30 Aug 2018

Maria Navascues-Cornago
Optometric Research Associate

Document reviewed and approved by: P Inwood Date: 31 Aug 2018

Michelle Inwood
Project Officer (Business Systems)

Document approved by: P Morgan Date: 31 August 2018

Philip Morgan
Director

Summary

This document describes a non-invasive method for the imaging and measurement of the height and cross-sectional area of upper and lower tear menisci using Optical Coherence Tomography (OCT).

Responsibilities

Clinical investigators or trained personnel would normally carry out this non-invasive procedure.

Equipment required

Topcon 3D-OCT 2000 (Topcon, Tokyo, Japan)

Computer

Procedures

Set-up

1. Switch on the computer and Topcon OCT instrument.
2. Remove dust cover and lens cap.
3. Clean the forehead-rest unit and chin-rest unit.
4. Mount the attachment for anterior segment onto the forehead rest.
5. Double-click the [3D OCT] icon on the desktop.
6. For a new subject, click the [Register New Patient] button. Enter the subject information in the dialogue box (ID) and click [Register]. The format of the ID will be study specific and the use of indefinable data should be considered.
7. For an existing subject, select the subject from the subject list or type the subject's details into the [Patient Search] panel and click the [Search] button.
8. Select subject from list and click the [Capture] button from the toolbar.
9. Operator should now look to the monitor screen on the OCT instrument.
10. Click on [set up] to confirm settings. [Anterior] tab and [Line Anterior Seg. 3.0mm].
    a. Scan Resolution [1024V]
    b. Color Photo: [OFF]
    c. Over Scan Count [Not].
    d. OCT Focus Position: [Cornea],
11. Exit the set up screen.

12. Select the [Anterior] tab.
13. Select the [Line Anterior Seg. 3.0mm] icon.
14. Select the [Scan ADJ LIVE] icon and use the arrows to rotate the green line until it is pointing down in a vertical position (if required).

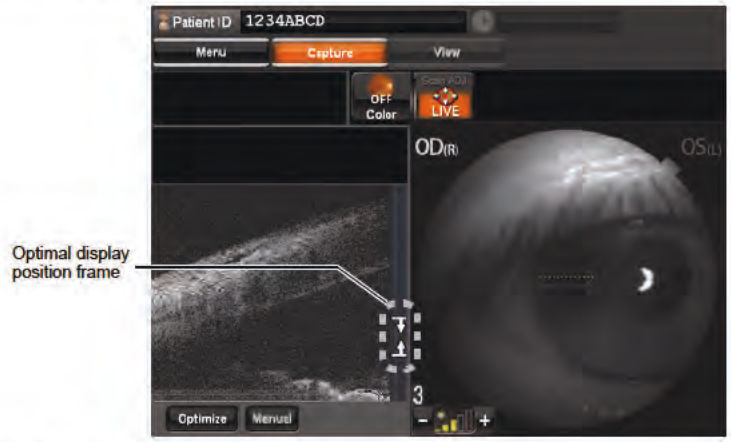
Positioning the subject

1. Subject is asked to place their chin on the chin-rest and the forehead against the rest.
2. Adjust the height of chin-rest if required (using buttons on OCT)
3. Instruct the subject to keep both eyes open during the procedure.

Capturing an image

1. Lower tear meniscus

a. The subject is asked to look straight ahead into the instrument.
b. Using the joystick, move the instrument body right/left and up/down to display the subject's eye at the centre of the anterior segment live image window (right side of the screen).
c. Using the joystick, adjust the height of the instrument, so the green vertical line crosses the lower meniscus at corneal 6 o'clock position
d. Using the joystick, move towards/away from the eye until a cross-section is observed on the OCT live image window (left side of the screen) The tear meniscus should be displayed within the 'Optimal display position frame' which is indicated by two white arrows displayed on the right side of the OCT live image window (see image below)



e. The focusing and image quality should be adjusted by moving the

instrument body.

f. When imaging the lower tear meniscus an “V” shaped image should be sought (the angle between the lower lid and the inferior cornea)
g. Make sure that the eyelashes are kept out of the picture.
h. After the subject blinks, adjust the focus briefly if needed, then press the joystick button to trigger image capture.
i. Three successful images (i.e. area of tear meniscus clearly defined) should be captured in this manner.
j. The images are automatically saved.

2. Upper tear meniscus

a. The subject is asked to look slightly upwards.
b. Using the joystick, adjust the height of the instrument, so the green dotted vertical line crosses the upper tear meniscus at corneal 12 o'clock position.
c. Using the joystick, move towards/away from the eye until a cross-section is observed on the OCT live image window. The tear meniscus should be displayed within the ‘Optimal display position frame’.
d. The focusing and image quality should be adjusted by moving the instrument body.
e. Make sure that the eyelashes are kept out of the picture.
k. When imaging the upper tear meniscus an “V” shaped image should be sought (the angle between the upper lid and the superior cornea)
l. After the subject blinks, adjust the focus briefly if needed, then press the joystick button to trigger image capture.
f. Three successful images should be captured.
g. The images are automatically saved.

Exporting an image

1. Select [View] on the toolbar.
2. Images should be exported in JPEG format. Select [Tools], [Options] and the [Export] tab. Select ‘JPEG Files’ from the [Export File Type] drop-down list and click [OK].
3. Select the image to be exported.
4. Click [Export] on the toolbar and select [B-Scan].
5. Enter the filename and click [Save].

Analysing an image

Image processing software such as ImageJ or customised MATLAB software can be used to process the images captured and measure the tear meniscus height and cross-sectional area.

Calculation of tear meniscus volume

If required, the upper tear meniscus volume (UTMV) and lower tear meniscus volume (LTMV) can be calculated as suggested by Palakuru et al. (2007):

UTMV = 25 mm of upper lid length X mm^2 of upper meniscus area X 1.294
LTMV = 25 mm of lower lid length X mm^2 of lower meniscus area X 1.294

References

1. TOPCON 3D-OCT 2000 USER MANUAL (Volume for instrument body). 3D OPTICAL COHERENCE TOMOGRAPHY. Version 8.2X (132 pages)*
2. TOPCON 3D-OCT 2000 USER'S MANUAL. 3D OPTICAL COHERENCE TOMOGRAPHY. PC SOFTWARE EDITION. Version 8.2X (264 pages)*
   *Copies of these Manuals (electronic only) can be found on the Server.
3. Palakuru JR, Wang J and Aquavella JV 2007. Effect of blinking on tear dynamics. *Invest Ophthalmol Vis Sci:* 48**;** 3032-7.

APPENDIX K: EUROLENS RESEARCH SOP #52, TEARLAB™

Eurolens Research

Clinical
Standard Operating Procedure

TearLab™

Gillian Howarth
Research Optometrist

First issued: v0; October 20, 2015
Current revision: v0; October 20, 2015
Reviewed (no changes): v0; July 3, 2018

Document control

Title:	TearLab™
Document type:	Clinical standard operating procedure
Number of pages:	5

Document author: C Howarth Date: 20 OCT 2015.
Gillian Howarth,
Research Optometrist

Document reviewed by: S Smith Date: 20 OCT 2015
Sarah Smith,
Research Optometrist

Document reviewed and approved by: P. Inwood Date: 20 Oct 2015
Michelle Inwood,
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Document approved by: P Morgan Date: 22 Oct 2015
Philip Morgan,
Director

Summary

Tears fulfill an essential role in maintaining ocular surface integrity, protecting against microbial challenge and preserving visual acuity.[1] Hyperosmolarity has been described in the literature as a primary marker of tear film integrity.[2] When either the quantity or quality of secreted tears is compromised, the total osmolarity of the tear film is increased due to increased evaporation. As a result, basal tear equilibrium is shifted to a saltier solution, which places stress on the corneal epithelia and conjunctiva.

The TearLab™ osmolarity system provides a quick and simple method for determining tear osmolarity using nanolitre volumes of tear fluid collected directly from the ocular surface.

Responsibilities

Clinical investigators or designated staff may use the TearLab™ osmolarity system.

Equipment

Procedure

Subject Testing Procedure

1. Turn the TearLab reader on.
2. Remove either pen from the reader. The LCD display will say “Ready”.
   NB do not collect tear samples if the display does not say “Ready”
3. Remove a test card from its package.
4. Attach a test card by sliding the wings of the test card onto the TearLab pen. The pen will light up and beep when the card is attached properly. The green light will stay on until you collect tears or the pen times out (after 2 minutes).
   IMPORTANT: Any test card that does not contain a protective sheath should not be used for subject testing.
5. Note the numeric code on the top of the test card.
6. Just before tear collection, whilst holding the test card wings, remove the protective sheath from the test card.
   NB ONLY collect tears if the green light is on. NEVER collect tears when the green light is off.

Tear Collection Procedure

1. Seat the subject with their chin tilted upward and eyes directed towards the ceiling.
2. Place one hand on the face for stabilisation. Do not pull the eyelid down or away from the eye.
3. Posiiton the tip of the pen above the lower eyelid.
4. Gently lower the pen until the bottom of the tip touches the thin line of moisture between the eyelid and the eye. It is not necessary to press inward towards the eye.
5. If the pen doesn’t beep immediately, withdraw the pen, ask the subject to blink, and restart the process.
6. The pen will beep and the green light turn off after a successsful tear collection.
7. Dock the pen into the reader within 40 seconds. Do not remove the test card from the pen before docking or all data will be lost.
8. Immediately press the RECALL key (it has a ‘U’ shaped arrow on it) below the up or down arrows to select the test card code (located on the top of the test card).
   NB it is important to select the code within 8 seconds to obtain an accurate result.
9. Press OK or wait 8 seconds for the reader to accept the code.

10. The reader will display the osmolarity result in a few seconds. This is then recorded by the investigator.
11. Remove the test card by pressing your thumb forward on top of the test card. Do not pull from the wings. Dispose in a biohazard container.

Quality Control

The blue electronic check card should be tested on each pen before each day of subject testing to ensure the system is performing within manufactured calibration specification.

To ensure the test cards are working and the test is being performed correctly a normal and high osmolarity control solution should be tested once with each lot number of test card or when a new shipment is received.

References

1. Schaumberg, DA, Sullivan, DA, Dana, MR et al, Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2: Basic Science and Clinical Relevance. *Advances in Experimental Medicine and Biology.* 1998; 438.
2. Definition and Classification of Dry Eye. Report of the Diagnosis and Classification Subcommittee of the Dry Eye Workshop (DEWS). *The Ocular Surface.* 2007;5(2):75-92.

TearLab™ Osmolarity System User Manual

Appendix A

TearLab™ Osmolarity System Quick Reference Guide (attached)
TearLab™ Osmolarity System Clinical Utility Guide (attached)

APPENDIX L: EUROLENS RESEARCH SOP #57, TEAR FLUID SAMPLING USING THE MICROCAPILLARY TUBE METHOD

Eurolens Research

Clinical
Standard Operating Procedure

Tear Fluid Sampling Using the Microcapillary Tube Method

Noor Haziq Saliman
PhD student

First issued: v0; October 20, 2015
Current revision: v0; October 20, 2015
Reviewed (no changes): v0; November 20, 2017

Document control

Title:	Tear Fluid Sampling using the Microcapillary Tube Method
Document type:	Clinical standard operating procedure
Number of pages:	5

Document author: _____ Date: 20 Oct 2015
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Document reviewed by: _____ Date: 20 OCT 2015
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Document reviewed and approved by: _____ Date: 20 Oct 2015
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Document approved by: _____ Date: 22 Oct 2015
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Director

Summary

Tear fluid collection can be obtained using a fine microcapillary tube for the biological investigation of tear content. Posa et al. (2013) reported that a microcapillary tube could sample higer number of proteins compared to a semi-invasive technique such as the Schirmer strip.

Collection of tear samples are useful to assess ocular surface disorder (OSD) by studying the proteins and other inflammatory biomarkers present in cases like dry eyes.

These guidelines describe the technique in which tear samples are collected using a microcapillary tube.

Equipment

Single-use, disposable, sterile, smoothly-polished, fine glass **microcapillary tubes and bulb assembly** to dispense collected tears into a LoBind protein microcentrifuge tube.

e.g. Wiretrol-Micropipettes, Drummond Scientific Co., Broomall, PA, USA. VWR cat # 53440-023 and 53507-268.

LoBind protein microcentrifuge tube to store tears.

e.g.Eppendorf™, North AmericaHauppauge, NY USA. VWR cat # 80077-232.

Procedure

1. A fluoroscein-free assessment of the eyes is first made using a slit lamp biomicroscope to ensure that there are no contraindications to conducting the procedure.
2. Tear collection should be performed without corneal anaesthesia.
3. Take a sterile capillary tube from its container for tear collection see Figure 1 (tubes are available in 2 µL, 5 µL and 10 µL).

Figure 1. Microcapillary tube

4. Ask the subject to sit in a chair.
5. Ask the subject to blink a few times, and then look away from the tear collector and the microcapillary tube.
6. Submerge the microcapillary tip at the lateral inferior tear meniscus, holding the microcapillary tube perpendicular to the lower lid margin as shown in Figure 2. This creates a suction which facilitates the flow of tears into the micropipette.

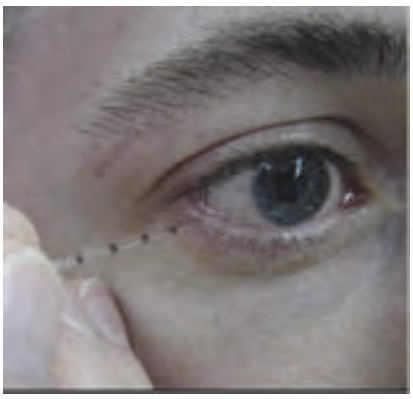

Figure 2. Tear collection

7. Care should be taken to ensure that the corneal surface is not touched during the tear collection procedure.
8. To avoid reflex tearing, touch the pipette tip in and out of the tear prism.
9. Subjects can blink and close their eyes for a few seconds during the tear collection procedure.
10. The time taken for drawing 4-5µL of the tear sample from each subject should be within 45 minutes. (The volume required may vary per protocol).
11. Following collection from the first eye, the entire volume should be carefully transferred/ejected into a labeled LoBind protein microcentrifuge tube using the bulb assembly. Ensure the whole droplet is at the bottom of the tube and the lid remains closed at all time.
12. Keep the microcentrifudge tube in a freezer at a temperature of -80°C until required for analysis.
13. Dispose of all used microcapillary tubes in the appropriate sharps container.

References

POSA, A., BRAUER, L., SCHICHT, M., GARREIS, F., BEILEKE, S. & PAULSEN, F. 2013. Schirmer strip vs. capillary tube method: non-invasive methods of obtaining proteins from tear fluid. *Ann Anat,* 195**,** 137-42.

APPENDIX M: EUROLENS RESEARCH SOP #41, LID MARGIN STAINING ASSESSMENT

Eurolens Research

Clinical
Standard Operating Procedure

Lid margin staining assessment

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Optometric Research Associate

First issued: v0; September 20, 2011
Reviewed (with changes): v1; February 28, 2014
Reviewed (no changes): v1; September 2, 2016
Reviewed (with changes): v2; March 2, 2017

Document control

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Document type:	Clinical standard operating procedure
Number of pages:	6

Document author: _____ Date: 2 MARCH 2017

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Document reviewed by: _____ Date: 2 MARCH 2017

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Document reviewed and approved by: _____ Date: 2 March 2017

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Document approved by: _____ Date: 2 March 2017

Philip Morgan

Director

Summary

The lid wiper is defined as that portion of the marginal conjunctiva of the eyelid that wipes the ocular surface during blinking. It has been shown that staining of this region of the upper eyelid has high specificity on defining non- and contact lens wearers with ocular discomfort.[1-3] It has also been shown that staining of the lower lid wiper is also present at similar levels in a symptomatic population.[4]

Responsibilities

Lid wiper epitheliopathy may form part of a typical biomicroscopic assessment routine and be performed by clinical investigators.

Definitions/Acronyms

Lid Wiper Epitheliopathy is often abbreviated as LWE or ULMS (Upper Lid Marginal Staining).

Procedure

Lid wiper epitheliopathy will be assessed at each lid margin: upper and lower, and in both eyes. Fluorescein and LIssamine Green staining will be assessed following the instillation routine detailed:

1. Apply one moistened fluorescein/lissamine green strip to the lower fornix of each eye.
2. After five minutes a second identical application should be instilled.
3. Examination of the upper and lower lid margins should be performed after a further minute.

How to grade

Lid wiper epitheliopathy will appear as depicted in Figure 1. Any staining present will then be graded according to the horizontal length and sagittal width of the total staining area.[3] These scales are depicted in

Table 1.

In the case of Figure 1 below, the horizontal length is over 9mm and would be graded 3. The sagittal width in Figure 1 is approximately 90% of the lid wiper and would also be graded 3. Therefore, on the CRF the grades for the right upper lid margin would be recorded as 3 and 3 respectively.

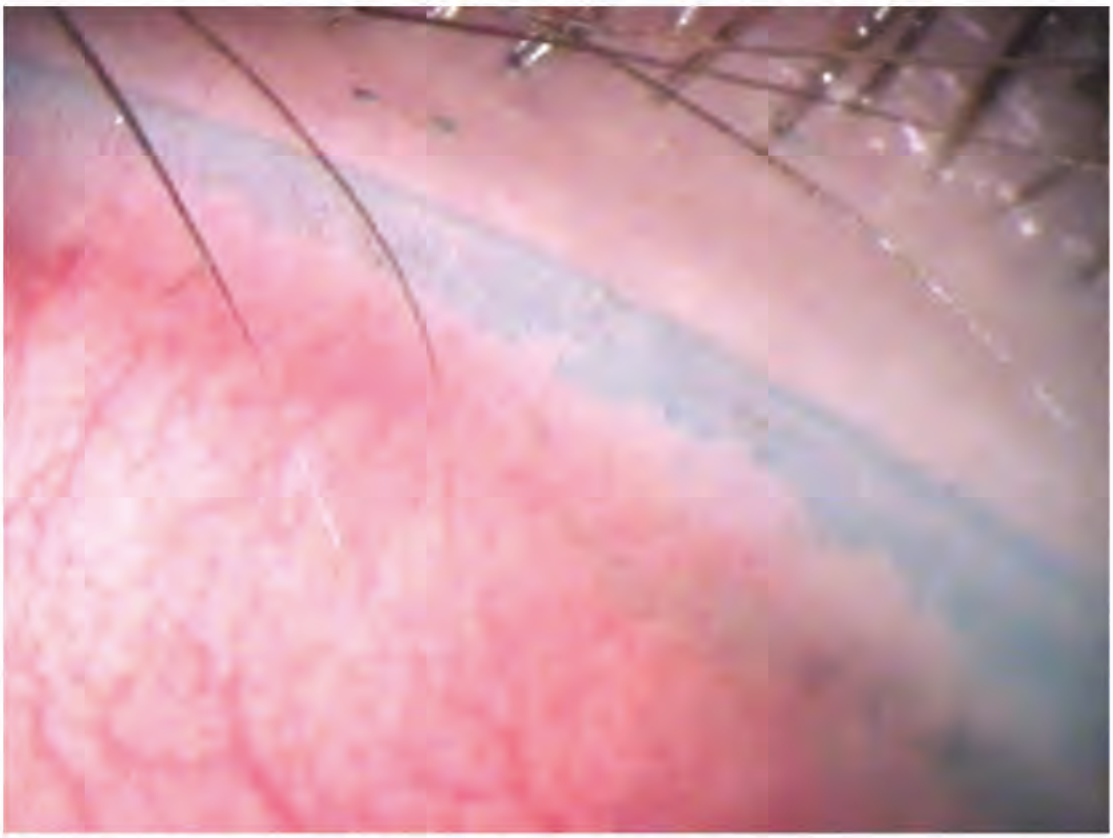

Figure 1: Lid wiper epitheliopathy appearance on upper lid margin.

Horizontal length (mm)	Average sagittal width (%)	Grade
<2mm staining	<25% of the width of wiper	0
2 - 4mm staining	25% to 50% of the width of wiper	1
5 – 9mm staining	51% to 75% of the width of the wiper	2
>9mm staining	>75% of the width of the wiper	3

Table 1: Grading scale for lid wiper epitheliopathy.

Advice for grading

Care should be taken to identify the line of staining denoting Marx's line as distinct from staining of the lid wiper area, as depicted in Figure 2.

If the staining of the lid margin is in more than one section, then take the total length when grading horizontal staining.

If the sagittal width of staining varies, then an average should be used.

Analysis purposes only

The graded scores from these two scales may be combined and an average severity score for each lid margin reviewed. The grading scale for the average severity score is depicted in Table 2. For example if horizontal length gave a severity of grade 2 and width a severity of grade 1, the average severity score will be recorded as 1.5 or Grade 2.[3]

Average LWE severity score	Grade
No LWE	0
Mild (0.25 – 1.00)	1
Moderate (1.25 – 2.00)	2
Severe (2.25 – 3.00)	3

Table 2: Grading scale for average lid wiper epitheliopathy score.

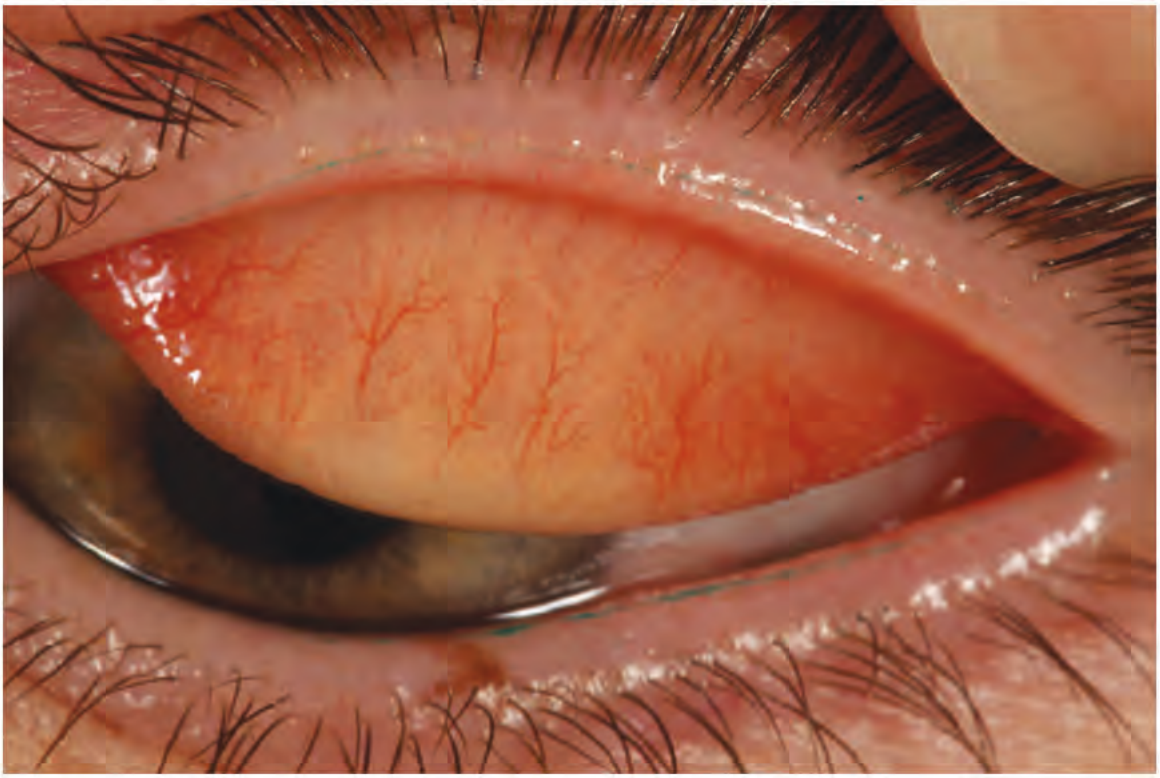

Figure 2: Staining of the line of Marx of the everted upper lid

Automated grading

Lissamine green staining can also be graded by automated or semi-automated analysis. Photographs of the upper and lower lid margins will be captured using a high quality digital camera (e.g. Canon EOS 7D or similar) mounted to a slit-lamp. Consistent camera exposure and illumination settings will be maintained during the study (typical camera settings are f-stop = 16, exposure = 1/250, ISO = 640 with an illumination setting of manual = 1/32). Polarising filters are typically used to minimise reflections in the images.

Images will be processed using custom-designed software developed in MATLAB. After manual delination of the lid margin, images will undergo image thresholding and binarisation in order to automatically detect lissamine green staining. The image analysis routine will extract the following variables:

- Area of lissamine green staining
- Intensity of lissamine green staining
- Overall staining index (area*intensity)

References

1. Korb, D. R. *et al*. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. *The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc* **28**, 211-216 (2002).
2. Korb, D. R. *et al*. Lid wiper epitheliopathy and dry eye symptoms. *Eye & contact lens* **31**, 2-8 (2005).
3. Korb, D. *et al*. Prevalence of lid wiper epitheliopathy in subjects with dry eye signs and symptoms. *Cornea* **29**, 377 (2010).
4. Guillon, M. & Maissa, C. Assessment of Contact Lens Wearers' Lid Margins With Lissamine Green. *ARVO Meeting Abstracts* **50**, 6343 (2009).

APPENDIX N: EUROLENS RESEARCH SOP #24 OBJECTIVE CONTACT LENS MEASURES

Eurolens Research

Clinical
Standard Operating Procedure

Objective Contact Lens Measures

Neil Chatterjee
Research Optometrist

First issued: v0; March 1, 2006
Reviewed (with changes): v1; December 6, 2011
Reviewed (with changes): v2; March 11, 2014
Reviewed (with changes): v2.1; October 11, 2016
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Document type:	Clinical standard operating procedure
Number of pages:	11

Document author: _____ Date: 22 October 2018
Neil Chatterjee
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Document reviewed by: _____ Date: 22 Oct 2018
Sarah Smith
Research Optometrist

Document reviewed and approved by: _____ Date: 22 Oct 2018
Michelle Inwood
Project Officer (Business Systems)

Document approved by: _____ Date: 22-Oct-2018
Philip Morgan
Director

Summary

Using this technique, the investigator can objectively measure contact lens fitting characteristics, such as movement and centration.

Equipment required:

- Slit lamp
- 0.2mm calibrated graticule eyepiece

Responsibilities

Objective contact lens measures may form part of a contact lens assessment and are performed by clinical investigators.

Definitions

Primary gaze movement: The change in position of the lens edge after a blink, while the subject is fixating in the primary gaze.

Upgaze movement: The change in position of the lens edge after a blink, while the subject is fixating in an upward gaze.

Primary gaze lag: The change in vertical position of the inferior lens edge from the resting primary gaze position, when the lower lid is pulled down.

Upgaze lag: The inferior decentration of the lens resulting from the subject changing fixation from primary to upward gaze.

Temporal gaze lag: The nasal decentration of the lens resulting from the subject changing fixation from primary to temporal gaze.

Nasal gaze lag: The temporal decentration of the lens resulting from the subject changing fixation from primary to nasal gaze.

Coverage: In a soft contact lens, the distance from the lens edge to the limbus. This can be defined both horizontally and vertically. Coverage may also be referred to as overlap.

Centration: For a soft lens, the optimum fitting position is about the centre of the cornea. Centration can be defined both horizontally and vertically.

Procedure

Setting up

1. Seat the subject comfortably at the slit lamp.
2. Ideally place the graticule eyepiece in the biomicroscope ocular which corresponds with the observer's dominant eye.

3. Focus the graticule eyepiece to the appropriate power.
4. Adjust magnification. Typically the magnification is set to 10x or 8x. However this will depend on the combination of graticule and slit lamp being used to ensure an observed measure corresponds to the same value in millimetres.
5. Diffuse illumination should be used when taking measurements.
6. It is important to instruct the subject to “look straight ahead”, when taking primary gaze movements. Any misalignment in fixation by the subject will cause the lens to decentre due to lag, which may affect measures.
7. All measurements should be made to the nearest 0.1mm.

Lens movement

Primary gaze movement

1. Instruct the subject to look straight ahead (eyes in the primary gaze position) and to continue blinking normally.
2. Turn the graticule vertically, the ball bearing should be in line with the lower edge of the scale. Align a mark on the scale with the lower edge of the lens.
3. If the lower lens edge is not visible, the bottom lid may be lowered slightly (without affecting the position of the lens), until the lower lens edge is visible. The primary gaze movement can then be measured by using the inferior lens edge.
4. During normal unforced blinking, measure the difference between the original lens edge position and the maximum displacement of the lens. This difference is the primary gaze movement of the lens.

Upgaze movement

1. Instruct the subject to look up and blink normally.
2. Align any mark on the graticule with the lower lens edge.
3. Observe the lens displacement occurring during normal unforced blinking. The maximum displacement noted is the measure of upgaze movement.
4. The lens may move both inferior and superior to the original position. The difference between these extreme positions is the measure of upgaze movement.

Lens lag

Primary gaze Lag

1. The subject is instructed to look straight ahead and not to blink.
2. Align any mark on the scale with the lower edge of the lens.

3. If the lower lens edge is not visible, the lowest visible edge of the lens should be observed.
4. The subject's lower eyelid is gently pulled down, so it is not supporting the contact lens. The lens will move slightly inferiorly, as it is no longer supported by the lower lid.
5. The difference between the lens in its primary position and the position of the lens with the lower lid pulled down is calculated. This is the primary gaze lag.

Upgaze Lag

1. Instruct the subject to look straight ahead (eyes in the primary gaze position) and not to blink.
2. The distance from the lower lens edge to the lower limbus is measured (inferior overlap primary gaze).
3. If the lower lens edge is not visible, the lower lid may be lowered slightly (without affecting the position of the lens), until the lower lens edge is visible.
4. The subject is then instructed to look up and not to blink. The distance from the lower limbus to the inferior lens edge is measured in upgaze (inferior overlap upgaze).
5. The change in eye position from primary to upgaze causes lens to decentre inferiorly, this decentration is the upgaze lag.
6. The upgaze lag can be calculated by:

   Upgaze lag = inferior overlap in upgaze – inferior overlap in primary gaze

Temporal gaze lag

1. Instruct the subject to look straight ahead (eyes in the primary gaze position) and not to blink.
2. The distance from the nasal lens edge to the nasal limbus is measured (nasal overlap primary gaze).
3. The subject is then instructed to look temporally and not to blink. The distance from the nasal limbus to the nasal lens edge is measured in temporal gaze (nasal overlap temporal gaze).
4. The change in eye position from primary to temporal gaze causes the lens to decentre nasally. This decentration is the temporal gaze lag.
5. The temporal gaze lag can be calculated by:

   Temporal gaze lag = nasal overlap in temporal gaze – nasal overlap in primary gaze

Nasal Gaze Lag

1. Instruct the subject to look straight ahead (eyes in the primary gaze position) and not to blink.
2. The distance from the temporal lens edge to the temporal limbus is measured (temporal overlap primary gaze).
3. The subject is then instructed to look nasally and not to blink. The distance from the temporal limbus to the temporal lens edge is measured in nasal gaze (temporal overlap nasal gaze).
4. The change in eye position from primary to nasal gaze causes the lens to decentre temporally. This decentration is the nasal gaze lag.
5. The nasal gaze lag can be calculated by:

   Nasal gaze lag = temporal overlap in nasal gaze – temporal overlap in primary gaze

Lens Position

Horizontal (x) coverage and centration

Nasal overlap O_N

Temporal overlap O_T

1. Instruct the subject to look straight ahead (eyes in the primary gaze position).
2. Turn the graticule horizontally. The scale should be almost bisecting the pupil horizontally.
3. At the vertical midpoint of the cornea, measure the horizontal distance from the lens edge to the limbus nasally. This value is the nasal overlap (or nasal coverage).
4. Reposition the graticule and measure the horizontal distance from the lens edge to the limbus temporally. This value is the temporal overlap (or temporal coverage).
5. Subtraction of the nasal value from the temporal value *and dividing by 2* gives the horizontal decentration (Appendix B). If the temporal overlap is greater than the nasal overlap, the value is **positive**. If the nasal overlap is greater than the temporal overlap, the value is **negative**. If the amount of overlap is equal nasally and temporally, the horizontal decentration is zero.

   Horizontal decentration= $(O_T - O_N)/2$

Vertical (y) coverage and centration

Superior overlap O_S

Inferior overlap O_I

1. Instruct the subject to look straight ahead (eyes in the primary gaze position).
2. With the graticule placed vertically, measure the distance from the lens edge to the limbus superiorly on the 90° meridian. This value is the superior overlap (superior coverage).
3. Reposition the graticule and measure from the limbus to the lens edge inferiorly on the 90° meridian. This value is the inferior overlap (inferior coverage).
4. Subtraction of the inferior value from the superior value *and dividing by 2* gives the vertical **decentration** of the lens. If the lens overlaps the limbus more superiorly than inferiorly, the value is **positive**. If the lens overlaps more inferiorly than superiorly, the value is **negative**. If the amount of overlap is equal superiorly and inferiorly, then the lens vertical decentration is zero.

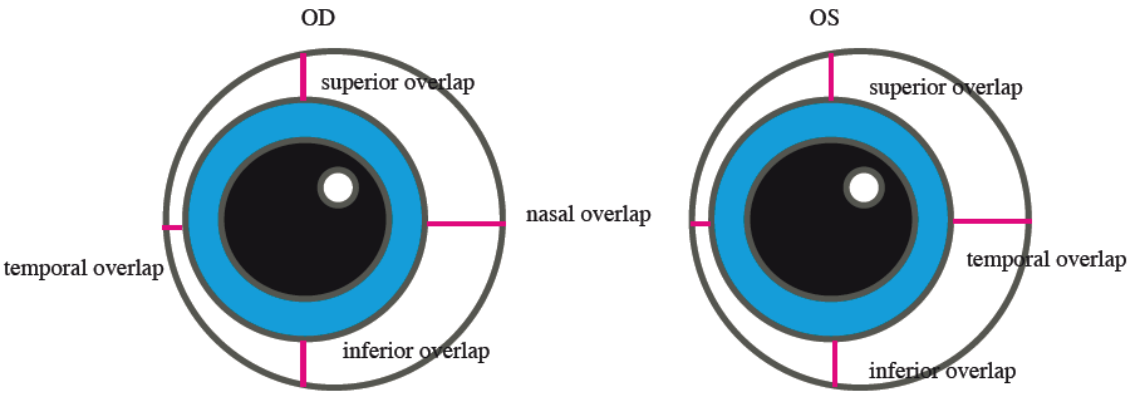
$$\text{Vertical decentration} = (O_S - O_I)/2$$

In many cases the upper and/or lower lens edges may not be visible when the subject's eyes are in the primary gaze position. In such cases, the lower lid may be lowered slightly (without affecting the position of the lens), until the lower lens edge is visible.

The superior measurement should be taken with the subject looking down slightly and the upper lid gently lifted to reveal the lens edge without altering the lens position.

Inferred results

Superior overlap in the primary position can be difficult to measure without disturbing the lens, due to anatomical difficulties. It is possible to infer an approximate value of superior overlap (and vertical decentration), if the overlap in the other three cardinal positions has been measured. Asymmetry of corneal and scleral topography accounts for some inaccuracy in this technique, although this is not thought to be clinically significant.



Nasal overlap	O_N
Temporal overlap	O_T
Total horizontal overlap	O_H
Superior overlap	O_S
Inferior overlap	O_I
Total vertical overlap	O_V

$O_N + O_T = O_H$

$O_S + O_I = O_V$

$O_H = O_V$

By substitution

$O_S = O_N + O_T - O_I$

Grading scale

1. Measurements should be made to the nearest 0.1mm and the decentration value should be written to the nearest 0.05mm. An example is shown below:

$$\text{Horizontal decentration} = \frac{1.0_{(T)} - 0.3_{(N)}}{2} = +0.35\text{mm}$$

2. To aid the investigator in recording these measurements, a crib sheet is available for most studies (see Appendix A). The spaces between the concentric circles record the distance between lens edge and limbus.
3. To aid the investigator, the clinical database can calculate lag and any decentration from these measurements.

Appendix A

Example of a lens fitting measurement sheet (see page 10). Note that the required measurements to be taken may vary between studies.

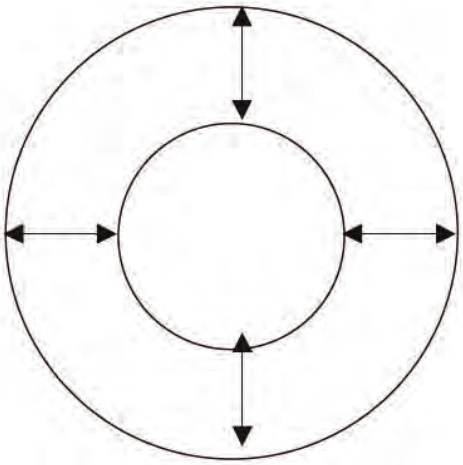
Appendix B

Calculation of decentration (see page 11).

Appendix A. Example of Graticule lens fitting form

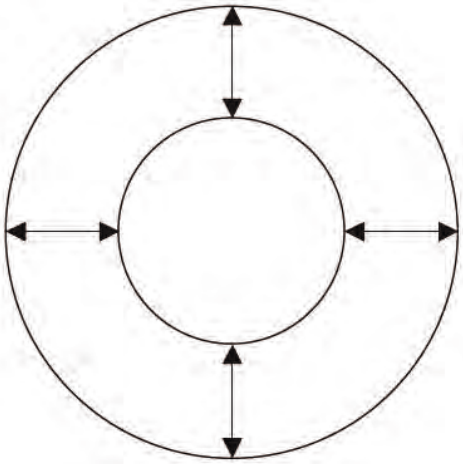
Lens fitting measurement sheet

RIGHT



Movement (primary position) =
Lens lag (primary position) =

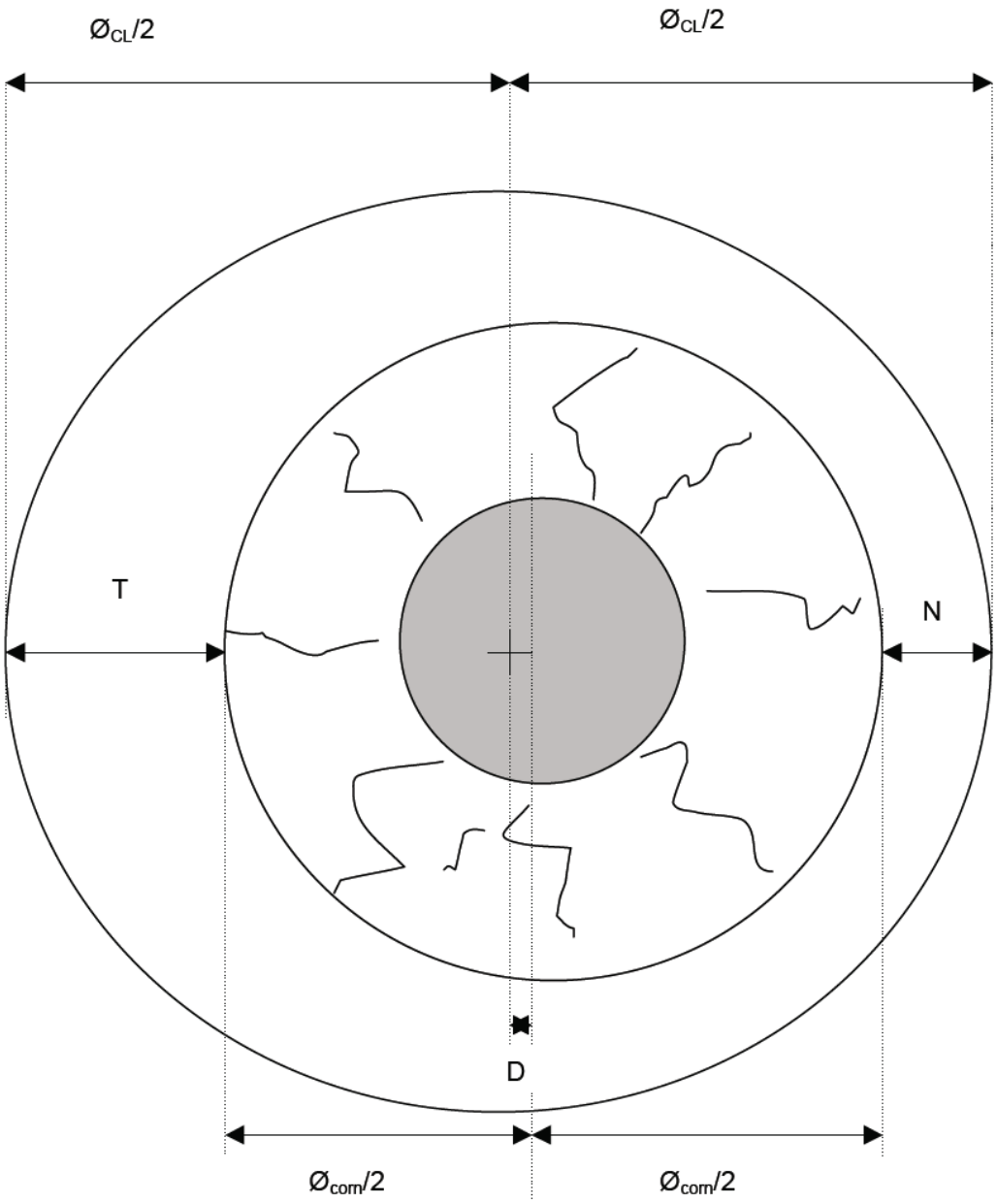
LEFT



Movement (primary position) =
Lens lag (primary position) =

Optometrist signature **Date**

Appendix B. Calculation of decentration



$Ø_{CL}/2 = T + Ø_{CORN}/2 - D$ AND $Ø_{CL}/2 = N + Ø_{CORN}/2 + D$

Therefore: $N + Ø_{CORN}/2 + D = T + Ø_{CORN}/2 - D$

Rearranging: $T - D = N + D$

$$D = \frac{T - N}{2}$$

APPENDIX O: [redacted] GUIDELINES FOR COVID-19 RISK MITIGATION

1.0 PURPOSE

The purpose of this document is to provide guidelines for the re-opening or initiation of clinical study sites participating in Johnson & Johnson Vision Care, Inc. (JJVCI) clinical studies during the COVID-19 pandemic.

2.0 SCOPE

This document provides guidelines for Johnson & Johnson Vision Care (JJVCI) to address the potential risks from COVID-19 to study subjects, investigators, study site staff, and monitors at study sites. The guidance provided in this document is in effect from the date of approval through the date of retirement of this Work Instruction. At a minimum, this Work Instruction will be reviewed and updated on a quarterly basis, as appropriate.

NOTE: Re-opening of sites outside of the US will be evaluated on a country by country basis subject to local health authority guidance.

3.0 DEFINITIONS

American Academy of Optometry (AAO): The American Academy of Optometry is an organization of optometrists based in Orlando, Florida. Its goal is to maintain and enhance excellence in optometric practice, by both promoting research and the dissemination of knowledge. The AAO holds an annual meeting, publishes a monthly scientific journal, gives credentials to optometrists through the fellowship process and publishes position statements.

American Optometric Association (AOA): The American Optometric Association, founded in 1898, is the leading authority on quality care and an advocate for our nation's health, representing more than 44,000 Doctors of Optometry (O.D.), optometric professionals, and optometry students. Doctor of Optometry take a leading role in patient care with respect to eye and vision care, as well as general health and well-being. As primary health care providers, Doctor of Optometry have extensive, ongoing training to examine, diagnose, treat and manage ocular disorders, diseases and injuries and systemic diseases that manifest in the eye. The American Optometric Association is a federation of state, student, and armed forces optometric associations. Through these affiliations, the AOA serves members consisting of optometrists, students of optometry, paraoptometric assistants and technicians. The AOA and its affiliates work to provide the public with quality vision and eye care.

Centers for Disease Control and Prevention (CDC): The Centers for Disease Control and Prevention is a national public health institute in the United States. It is a United States federal agency, under the Department of Health and Human Services, and is headquartered in Atlanta, Georgia.

COVID-19: Current outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

Clinical Study: Voluntary research studies conducted in people and designed to answer specific questions about the safety or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments. May also be called clinical trials, studies, research, trials, or protocols.

Clinical Study Site: Location where a clinical study is conducted, such as a doctor's office, university, or laboratory. Clinical studies are conducted by Investigators who are individual(s) responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals, the Investigator is the responsible leader of the team and may be called the Principal Investigator.

Clinical Operations Manager (COM): The Johnson & Johnson Vision Care (JJVCI) individual responsible for the overall management of a clinical trial.

Monitor: An individual designated to oversee the progress of a clinical study and ensure that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

Medical Safety Officer (MSO): Physician who has primary accountability in their product portfolio for product health and safety, and who serves as an independent medical voice for patient safety.

Safety Management Team (SMT): A cross-functional, collaborative team responsible for review, assessment and evaluation of medical safety data arising from any source throughout the product life cycle.

4.0 GUIDANCE FOR STUDY DOCUMENTS

In alignment with recent health authority guidance, JJVCI is providing recommendations for study-related management in the event of disruption to the conduct of the clinical study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health, safety and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted as outlined in the protocol.

During the COVID-19 pandemic, the additional risks listed below need to be considered for study participants and study personnel:

4.1 Additional Risks Related to the COVID-19 Pandemic:

- The possible transmission of the Coronavirus infection and consequent complications, beyond the risk of adverse events due to the investigational device and/or procedures.
- The risk may be higher in an optometric clinical study because of the close contact the subject will have with health care professionals during the procedures and assessments (since the investigator must make the measurements close to the subject's face) and, in addition the need for multiple follow-up visits/exams which may expose the subject to other patients and/or healthcare professionals who might be transmitting the virus, even if they do not have symptoms.
- Potential disruptions to the study may be necessary due to current or future pandemic-related emergency restrictions, which may lead to delays in scheduled follow-up visits.
- Subjects experiencing an adverse event related to contact lens wear may receive delayed treatment due to COVID-19 restrictions. In this event, all assessments that can be conducted virtually will be completed by the investigator to determine the best course of treatment for the subject, including an unscheduled visit, up to discontinuation from the study, as appropriate.

If a study subject is found to have contracted COVID-19 during participation in a study, he/she will be discontinued from the study and followed until COVID-19 Adverse Event (AE) resolution.

To help minimize the above potential risks, JJVCI recommend reviewing/complying with local, state, and governmental guidance for COVID-19 risks.

JJVCI will provide the following study specific documents with language pertaining to COVID-19 risks:

4.1.1 Informed Consent:

Will include information concerning the study-associated risks related to the COVID-19 pandemic in bold font and/or boxed on the first page of the Informed Consent document:

STUDY ASSOCIATED RISKS RELATED TO COVID-19 (CORONAVIRUS) PANDEMIC

It is important to note that this study will be conducted, at least in part, during the COVID-19 pandemic. As such, additional risks associated with the infection with COVID-19 exist for you. This is particularly important for this study due, in part, to the closeness of the doctor during the study examinations.

The potential effects of the disease are not fully known, at this time, and may include long-term serious health consequences. In severe cases, this may result in hospitalization and/or death. Based on current knowledge from the Centers for Disease Control and Prevention (CDC), those at high-risk for severe illness from COVID-19 include older adults and people with underlying medical conditions.

During this study, all appropriate measures will be taken to minimize risks including the use of personal protective equipment such as masks and gloves, as well as proper sanitization. This is in conformance to guidance from the CDC, local health departments, and the state and county in which the study doctor's office is located. However, these measures may not completely eliminate the risks associated with contracting COVID-19.

If you are found to have contracted COVID-19 or feel ill with flu-like symptoms during participation in the study, you will not be permitted to continue in-office study follow-up visits, but you will receive instructions and your condition will be monitored by the doctor and/or study staff.

4.1.2 COVID-19 Risk Control Checklist:

Will include COVID-19 risk control methods that are required by a site to conduct JJVCI clinical studies. The risk controls are consistent with CDC, AOA, AAO Guidance. The Principle Investigator will review/sign the study specific checklist prior to the Site Initiation Meeting.

Study Number
Site Number
Principal Investigator (PI) Name

The following COVID-19 risk control methods are required to conduct Johnson & Johnson Vison Care clinical studies. Please review the following requirements and Initial each requirement.

PI Initials	General Site Safety Planning Measures
	Signage within site describing Risk Control methods
	Social Distancing practices throughout site (waiting rooms, lobby, exam rooms, etc.)
	Non-contact thermometer available to assess temperatures of staff and patients
	Training on patient flow and physical distancing in waiting room
	Establish longer time frame between patient appointments to reduce persons in the site
	Staff should receive job-specific training on PPE and demonstrate competency with selection and proper use of PPE and wear at all times during interactions with subjects (e.g., putting on and removing without self-contamination)

PI Initials	Site Staff Daily Safety Measures
	As part of routine practice, site staff should regularly monitor themselves for fever and symptoms of COVID-19, including temperature checks
	Any staff member (including Investigators) showing signs of being sick or testing positive for COVID-19 should not be permitted to work and the Sponsor shall be informed **NOTE: Inform JJVC in 24 hours of any significant impact to the study.**
	Ensure that all staff wear a mask Gloves should be required when working directly with patients and changed between each patient

	Have staff thoroughly wash hands for at least 20 seconds or use an alcohol-based hand sanitizer when they arrive, before and after each patient, before eating and after using the bathroom.
	Cleaning and disinfection procedures for exam rooms and instruments or equipment between patients with gloves.
	Cleaning and disinfection procedures for commonly touched surfaces (doors, chairs, computers, phones, etc.) with gloves.

PI Initials	Before a Patient or Study Visit:
	Patients should be asked prior to entering the site about fever and respiratory illness and whether they or a family member have had contact with another person with confirmed COVID-19 in the past 14 days. Patients exhibiting signs of being sick should be rescheduled when their symptoms resolve.
	Instruct patients that companions should remain outside of the facility and not accompany the patient into the facility unless they are a parent/guardian of the patient or if they are a true caregiver and need to assist the patient
	Request the patient to call or text the office upon arrival so entrance to and movement through facility can be coordinated by site staff

PI Initials	Patients Entering the site:
	Temperature checks utilizing a non-contact thermometer for all patients and companions entering the site.
	All patients and companions must wear cloth or disposable mask at all times in the site
	Maintain social distancing. Waiting rooms or lobbies should be as empty as possible. Advise seated patients to remain at least 6 feet from one another.
	Communal objects in (e.g. toys, reading materials, etc.) should be removed or cleaned regularly.

I certify that I have read and agree to implement all the listed COVID-19 Risk Control Measures required for the conduct of Johnson & Johnson Vision Care studies.

Principal Investigator Signature and Date

RESOURCE LINKS

US Resource Links

- OSHA Training
  https://www.osha.gov/SLTC/covid-19/controlprevention.html

  Personal Protective Equipment (PPE) Training
  CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html

- I&R Training
  ACUVUE® LensAssist: https://www.acuvue.com/lensassist

- Clinic Preparedness Guides
  CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinic-preparedness.html
  AOA: https://aoa.uberflip.com/i/1240437-aoa-guidance-for-re-opening-practices-covid-19/1?m4=
  American Optometric Association: https://www.aoa.org/optometry-practice-reactivation-preparedness-guide

- In-Office Disinfection of Multi-Patient Use Diagnostic Contact Lenses
  https://www.gpli.info/wp-content/uploads/2020/03/2020-01-15-in-office-disinfecting-of-diagnostic-lenses.pdf

OUS Resource Links

- Updates on local regulations in Hong Kong
  https://www.coronavirus.gov.hk/eng/index.html

- Resumption of optical services in England: Letter from Matt Neligan and Poonam Sharma
  https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0601-reopening-of-optical-services-letter-17-june-2020.pdf

- NHS Optical Letter
  https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0127-optical-letter-1-april-2020.pdf

- The College of Optometrists primary eye care COVID-19 guidance: Red phase
  https://www.college-optometrists.org/the-college/media-hub/news-listing/coronavirus-covid-19-guidance-for-optometrists.html

- The College of Optometrists COVID-19: College updates
  https://www.college-optometrists.org/the-college/media-hub/news-listing/coronavirus-2019-advice-for-optometrists.html#CollegeGuidelines

4.1.3 Protocol Compliance Investigator(s) Signature Page:

Will include a statement indicating that the Principal Investigator (PI) agrees to conduct the study in compliance with all local, state, and governmental guidance's for COVID-19 risk mitigation.

I have read the suggested guidance provided by JJVCI pertaining to the COVID-19 risk mitigation, (COVID-19 Work Instruction in the Appendix of this protocol). I agree to conduct this study in compliance with local, state, governmental guidance for COVID-19 risks.

4.1.4 Study Site Initiation Training Slides:

Will include suggestions to help mitigate potential transmission of COVID-19. Suggestions may include maintaining social distancing in the clinical site by staggered scheduling of study patients, wearing proper PPEs, frequent disinfection, and installing shields on the slit lamp and other applicable equipment.

5.0 GUIDANCE FOR REMOTE SUBJECT VISITS

Potential disruptions to the study may be necessary due to current or future pandemic-related emergency restrictions. Possible disruption of the study as a result of COVID-19 control measures may lead to delays in scheduled follow-up visits.

Subjects may be delayed in being seen for study follow up visit(s), for example due to COVID-19 control measures or due to the subject's concerns or fears about COVID-19 risk. When appropriate, the remote assessment will be conducted to the extent possible. Discussions with the subject during remote assessments may include:

Procedure	Details
Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire regarding the test article when applicable and feasible.
Change of Medical History (Adverse Events) and Concomitant Medications / Therapies Review	Record any adverse events or medical history changes from the previous study visit with the subject/parents. Review the subject's concomitant medications/therapies and record any changes from the previous study visit.
Wearing Time and Compliance	Record the average wearing time (including number of hours per day during weekdays and weekends, and number of days per week). Confirm compliance with the prescribed wear schedule. • Record and discuss the lens wear compliance based on the subject's self-report. For example, the subjects will be asked the time of the day the subject typically puts on the study lenses in the morning and takes off in the evening, the number of days per week lenses were worn, and the number of consecutive days the subject didn't wear the study lenses, etc.

The discussion with the subject will be documented in EDC under Tele-Visit and a minor protocol deviation will be noted. If during the telephone consultation, a subject states he/she wishes to discontinue participating in the study, instruct the subject to stop wearing the study lenses and schedule the subject to return to the clinic for a Final Evaluation at the at earliest possible time. Subjects should return all unused lenses to the clinic at the last visit.

Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing data, including data related to protocol-specified procedures. Case report forms should capture specific information regarding the basis of missing data, including the relationship to the COVID-19 pandemic.

6.0 STUDY CONDUCT DURING PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including Optometry Clinics; and changes in clinic procedures required to address the COVID-19 challenge.

Every effort should be made to adhere to protocol-specified assessments for study participants, including follow-up. However, if scheduled visits cannot be conducted in person at the study site it is suggested that assessments be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed in order to continue participant monitoring in accordance with the protocol where possible. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible.

Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Interruptions of test article wear or discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical monitor to discuss initial plans for study intervention and follow-up. The medical monitor will notify the Safety Management Team of any subject(s) that have reported "COVID-19", "Asymptomatic COVID-19", or "Suspected COVID-19" adverse events within 24 hours of the notification.

Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

COVID-19 screening procedures that may be mandated by local healthcare systems do not need to be reported as an amendment to the protocol even if done during clinical study visits.

6.1 Monitoring Visits

When on-site monitoring by the sponsor is not feasible, the sponsor's site monitor will contact the study site to schedule remote visits. In such cases, on-site monitoring visits will resume when feasible, with increased frequency to address the source data verification backlog.

Even with staffing limitations during this COVID-19 pandemic, all routine operations related to clinical trials should be well-documented and archived as part of standard process. When conditions permit, all parties involved in this clinical trial should communicate relevant information in a timely manner so that all relevant parties remain sufficiently informed.

6.1.1 Study Site Initiation:

During the period that this Work Instruction is in effect, Site Initiation Meetings and training of study site staff will be conducted remotely. The JJVCI study team will conduct training via Skype, Zoom, Microsoft Teams or similar software as well as utilize online training materials, as applicable. Study site training will be documented utilizing Site Initiation Report (Form Control No. [redacted] per Study Site Initiation (Form Control No. [redacted].

On-site visits may be considered when, for example, hands-on training or evaluation of site facilities is required. While on site, the Clinical Research Associate (CRA) will follow all local, state, and governmental policies for COVID-19 Risk Mitigation, including social distancing, wearing of PPE, etc. as applicable for the location of the study site.

6.1.2 Interim Monitoring Visits (if applicable):

During the period that this Work Instruction is in effect, Interim Monitoring On-site visits will be kept to a minimum and include only those tasks that the CRA cannot perform remotely (e.g., source document verification, test article reconciliation, etc.).

To ensure data integrity during the conduct of all JJVC studies, clinical study teams will follow the study specific Clinical Monitoring Plan (Form Control No. [redacted]

While on site, the CRA will follow all local, state, and governmental policies for COVID-19 Risk Mitigation, including social distancing, wearing of PPE, etc. as applicable for the location of the study site.

6.1.3 Study Site Closure:

During the period that this Work Instruction is in effect, the duration of the Study Site Closure Visit will be limited to tasks that the CRA cannot perform remotely (e.g., source document verification, test article final reconciliation and return, etc.).

Attachment A: Study Site Correspondence

XXXX XX, 2020

Re: COVID-19 Mitigation Plan, <<CR-xxxx/protocol title>>

Dear <<Principle Investigator>> and Study Team,

Coronavirus (COVID-19) has impacted several communities and business activities over the past several months. While we work toward the successful conduct of clinical studies, our commitment continues to be the safety of patients, healthcare professionals, and to our communities.

Therefore, we would like to share the following revisions/additions related to the above referenced Johnson & Johnson Vision Care company sponsored clinical trial(s) you are currently working on or considering participation within.

Protocol:

- Guidelines for COVID-19 Risk Mitigation provided in the Appendix section.

Protocol Signature Page:

- Will include a statement indicating the Principle Investigator agrees to conduct the study in compliance with all local, state, and governmental guidelines for COVID-19 risk mitigation.

Informed Consent:

- Will include information concerning the study-associated risks related to the COVID-19 pandemic in bold font and/or boxed on the first page of the Informed consent document.

COVID-19 Risk Control Checklist for Clinical Studies:

- Will include COVID-19 risk control measures that are required to ensure the safety and health of subjects, site staff and monitors during the pandemic.

We want to encourage the need for open lines of communication about potential challenges you may foresee as the result of the current COVID-19 situation. Therefore, we encourage you to regularly connect with your respective Johnson & Johnson clinical study team (Clinical Research Associate (CRA), Lead CRA or Study Managers).

Thank you for your continued engagement, collaboration, and dedication to your study subjects during this challenging time.

Please file this letter in your site file study correspondence.

Clinical Study Protocol
Johnson & Johnson Vision Care, Inc.

PROTOCOL COMPLIANCE INVESTIGATOR(S) SIGNATURE PAGE

Protocol Number and Title: CR-6290 Late Night Study 2: End-of-Day Assessment of Asymptomatic and Symptomatic Soft Lens Wearers

Version and Date: v6.0 Amendment 5, 23 September 2020

I have read and understand the protocol specified above and agree on its content.

I agree to conduct this study according to ISO 14155,[1] GCP and ICH guidelines,[2] the Declaration of Helsinki,[3] United States (US) Code of Federal Regulations (CFR),[4] and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations. The Principal Investigator is responsible for ensuring that all clinical site personnel, including Sub-Investigators adhere to all ICH[2] regulations and GCP guidelines regarding clinical trials during and after study completion.

I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I am responsible for ensuring that all clinical site personnel including Sub-Investigators adhere to all ICH[2] regulations and GCP guidelines regarding clinical trials during and after study completion.

All clinical site personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all clinical site personnel involved in the conduct of this study are informed about their obligations in meeting the above commitments.

I shall not disclose the information contained in this protocol or any results obtained from this study without written authorization.

I have read the suggested guidance provided by JJVCI pertaining to the COVID-19 risk mitigation, (COVID-19 Work Instruction in the Appendix of this protocol). I agree to conduct this study in compliance with local, state, governmental guidance for COVID-19 risks.

Principal Investigator:

_____ _____

Signature Date

_____

Name and Professional Position (Printed)

Institution/Site: _____

Institution/Site Name

_____

Institution/Site Address