JOHNSON & JOHNSON VISION CARE, INC.

Clinical Study Protocol

An investigation of the impact of localized topical anesthesia of the ocular surface on end-of-day contact lens discomfort

Protocol CR-6292 [redacted]

Version: 1.0

Date: 24 September 2018

Investigational Products: Proxymetacaine hydrochloride 0.5%, Sodium chloride 0.9%

Key Words: anesthesia, eyelid margin, cornea, contact lens comfort, end-of-day, symptomatic, non-dispensing, daily wear

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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PROTOCOL TITLE, NUMBER, VERSION

Title: An investigation of the impact of localized topical anesthesia of the ocular surface on end-of-day contact lens discomfort.
Protocol Number: CR-6292 [redacted]
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Date: 24 September 2018

SPONSOR NAME AND ADDRESS

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

MEDICAL MONITOR

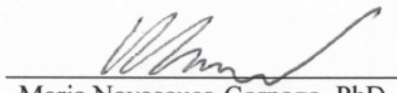
Name: Kristy Canavan
Title: Senior Principal Research Optometrist
Address: 7500 Centurion Parkway, Suite 100, Mail W-2A, Jacksonville, FL 32256
[redacted]

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	 Maria Navascues-Cornago, PhD Research Associate, The University of Manchester Michael Read (manager of Maria Navascues-Cornago) signing on behalf of	27th September 2018 DATE
Study Responsible Clinician	See Electronic Signature Report Kristy Canavan OD Senior Principal Research Optometrist, JJVC	DATE
Clinical Operations Manager	See Electronic Signature Report [redacted]	DATE
Biostatistician	See Electronic Signature Report [redacted]	DATE
Reviewer	See Electronic Signature Report [redacted]	DATE
Data Management	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	Maria Navascues-Cornago	Original Protocol	24 September 2018

SYNOPSIS

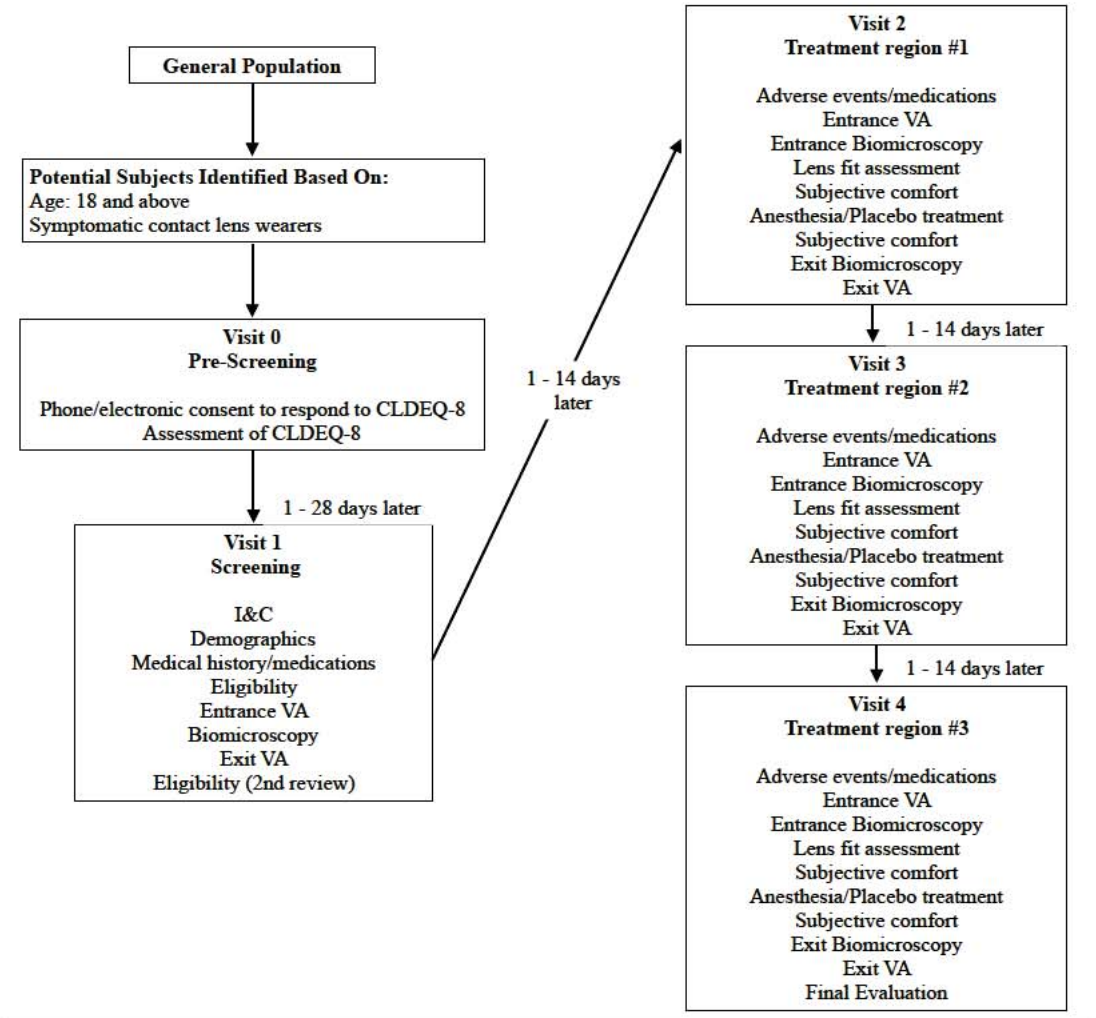
Protocol Title	An investigation of the impact of localized topical anesthesia of the ocular surface on end-of-day contact lens discomfort.
Sponsor	JJVC, 7500 Centurion Parkway, Jacksonville, FL 32256
Clinical Phase	Development phase, phase 0
Trial Registration	This study will be registered on ClinicalTrials.gov
Test Article(s)	None (habitual contact lenses)
Wear and Replacement Schedules	Habitual lenses will be worn for 14 ± 2 hours on study days
Objectives	Primary Objective To evaluate the effect of topical anesthesia of the upper lid margin, lower lid margin and cornea on end-of-day discomfort in symptomatic contact lens wearers. Secondary Objective To determine the effect of contact lens removal on end-of-day discomfort in symptomatic soft contact lens wearers.
Study Endpoints	Primary endpoint: Subjective scores of comfort (VAS scale) collected at various time points: • Immediately prior to lens application • 5 minutes after lens application • 14 hours after lens application (i.e. pre-treatment) • Immediately after lens removal prior to treatment application, only for the cornea. • 5 minutes post-treatment • 10 minutes post-treatment Other observations: none.

Study Design	This is a controlled, randomized, subject-masked, 3x3 crossover, non-dispensing, contralateral study. Twenty subjects will be recruited based on their scores (with their habitual lenses) from the Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8 score of 20-37) and examined on four occasions: Visit 1: Screening Visit 2-4: At each study visit, an ocular region (upper lid margin, lower lid margin or cornea) will be anesthetized on one eye, whilst the fellow eye will receive a saline placebo treatment at the same ocular location. Subjective comfort scores (VAS scale) will be collected prior to and following the treatment on each eye. 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	Up to 20 eligible subjects will be enrolled into the study with a target of 15 to complete.
Study Duration	Five months
Anticipated Study Population	Habitual soft contact lens wearers aged 18 and above who are classified as symptomatic based on a CLDEQ-8 score of 20-37
Eligibility Criteria	Potential subjects must satisfy all of the following criteria to be enrolled in the study: Inclusion Criteria after Screening 1. They are of legal age (18 years) and capacity of volunteer. 2. The subject must read, understand, and sign the STATEMENT OF INFORMED CONSENT and receive a fully executed copy of the form. 3. They must appear able and willing to adhere to the instructions set forth in this clinical protocol. 4. They have worn the same brand of soft spherical contact lenses for at least the previous three months, by self-report. 5. They are defined as 'symptomatic' contact lens wearers (CLDEQ-8 score of 20-37) with their habitual contact lenses. 6. They are willing to wear their lenses for approximately 14 hours on study days. 7. They have a wearable pair of spectacles, if applicable. 8. They agree not to participate in other clinical research

	for the duration of this study. Inclusion Criteria after Baseline 9. They can attain high contrast logMAR visual acuity of 0.20 or better in their habitual contact lenses in each eye. 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. They are using any topical medication such as eye drops or ointment. 4. They have had cataract or corneal refractive surgery. 5. They are pregnant or breast-feeding by self-report. 6. They have any infectious disease (e.g. hepatitis) or any immunosuppressive disease (e.g. HIV), by self-report. 7. They have any known hypersensitivity or allergic reaction to any of the known ingredients in the anesthetic. 8. They have a history of severe allergic reaction or anaphylaxis. 9. They have a history of cardiac disease or hyperthyroidism. 10. They have taken part in any other contact lens or care solution clinical trial or research, within two weeks prior to starting this study. 11. They are an employee or immediate family member of an employee of clinical site (e.g., Investigator, Coordinator, Technician). Exclusion Criteria after Baseline 12. They have any corneal distortion resulting from previous hard or rigid lens wear or have keratoconus. 13. They have grade 3 or greater of any of the following ocular surface signs which would contraindicate contact lens wear: corneal oedema, corneal vascularisation, corneal staining, tarsal conjunctival changes or any other abnormality which would normally contraindicate contact lens wear.

Disallowed Medications/Interventions	No ocular topical medications 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
Measurements and Procedures	Subjective comfort scores (VAS scale) and safety parameters (visual acuity and biomicroscopy)
Microbiology or Other Laboratory Testing	None
Study Termination	The occurrence of one or more Unanticipated Serious Adverse Device Effect (USADE), or any SAE where relationship to study agent cannot be ruled out, will result in stopping further study procedures. In the event of a UADE or SAE, the Sponsor Medical Monitor may unmask the treatment regimen of subject(s) and may discuss this with the Principal Investigator before any further subjects are enrolled.
Ancillary Supplies/ Study-Specific Materials	Topical anesthetic: proxymetacaine hydrochloride 0.5% (Chauvin Pharmaceuticals Ltd) Crest Medical Ltd Saline Pods (or other sponsor-approved material)
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



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
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
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VA	Visual Acuity

1. INTRODUCTION AND BACKGROUND

Previous work [redacted] has shown that we are able to successfully and selectively anesthetize the entire cornea, upper lid margin and lower lid margin in the majority of subjects whilst keeping the other ocular regions relatively unaffected. Isolating specific regions of the anterior ocular surface in this manner is potentially useful for systematically investigating whether or not contact lens discomfort can be improved when any of these areas are 'numbed'.

The aim of this study is to evaluate the effect of topical anesthesia on the upper eyelid margin, lower eyelid margin and the cornea in wearers suffering from end-of-day contact lens discomfort.

1.1. Name and Descriptions of Investigational Products

The following products will be used in this study:

- Single use Minims of proxymetacaine hydrochloride, 0.5% (a commercially available topical anesthetic) will be used to temporarily numb selective areas of the ocular surface (lower lid margin, upper lid margin and cornea).
- Sodium chloride 0.9% will be used as a placebo treatment.

1.2. Intended Use of Investigational Products

The intended use of proxymetacaine hydrochloride, 0.5% is to numb selective areas of the ocular surface. It is a topical ocular anesthetic. Typically, a drop which is ~30µl in size is used to numb the cornea in everyday clinical practice but in this work smaller amounts than this will be used in one eye on three different study days. The amounts used are detailed in the Eurolens Research Standard Operating Procedure 'Procedure for selectively anaesthetizing the cornea and eyelid margins' (Appendix D).

Sodium chloride 0.9% will be used as a placebo treatment in one eye on three different study days.

1.3. Summary of Findings from Nonclinical Studies

Not Applicable – Marketed product only.

1.4. Summary of Known Risks and Benefits to Human Subjects

There is no direct benefit to the subject from participation in the study. The information obtained from this study will aid in the development of improved contact lenses in the future.

Proxymetacaine hydrochloride, 0.5%: see electronic Medicines Compendium (eMC) entry for this drug (Summary of Product Characteristics) and the Patient Information leaflet in Appendix C.

Sodium chloride 0.9%: see Material Safety Data Sheet in Appendix C.

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

One previously completed sponsored clinical study:

Navascues-Cornago M. *Clinical Study Report #(VIS-CR-5876) Project Lennon: Understanding Contact Lens Comfort.* June 6, 2017. [6]

Also, previous pilot wok on anesthetizing parts of the ocular surface was presented at the following conference:

Navascues-Cornago M, Maldonado-Codina C and Morgan PB. Effect of selective topical anesthesia on initial comfort of rigid contact lenses. British Contact Lens Association 39th Annual Clinical Conference and Exhibition. May 29-31, 2015, ACC, Liverpool, UK.[7]

2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Objectives

Primary Objective
To evaluate the effect of topical anesthesia of the upper lid margin, lower lid margin and cornea on end-of-day discomfort in symptomatic contact lens wearers.

Secondary Objective
To determine the effect of contact lens removal on end-of-day discomfort in symptomatic soft contact lens wearers.

2.2. Endpoints

Primary Endpoint(s)
The primary endpoint is the subjective scores of comfort (VAS scale) collected at various time points:

- Immediately prior to lens application
- 5 minutes after lens application
- 14 hours after lens application (i.e. pre-treatment)
- Immediately after lens removal prior to treatment application, only for the cornea.
- 5 minutes post-treatment
- 10 minutes post-treatment

2.3. Hypotheses

Primary Hypotheses

1. Post-treatment subjective scores of comfort (VAS scale) for anesthetized eyes are superior to eyes that received the placebo for at least one of the ocular regions (upper lid margin, lower lid margin, or cornea).
2. Comfort change from pre-treatment for anesthetized eyes is superior to eyes that received the placebo for at least one of the ocular regions (upper lid margin, lower lid margin, or cornea).
3. Post-treatment subjective scores of comfort (VAS scale) for anesthetized eyes are equivalent to 5-minute post lens application levels in the morning for at least one of the ocular regions (upper lid margin, lower lid margin, or cornea). An equivalence margin of 10 points will be used.

Secondary Hypotheses

1. Post-treatment subjective scores of comfort (VAS scale) for eyes with the cornea anesthetized are superior to eyes with the upper or lower lid margins anesthetized.
2. Comfort change from pre-treatment for eyes with the cornea anesthetized is superior to eyes with the upper or lower lid margins anesthetized.
3. Subjective scores of comfort (VAS scale) at lens removal are equivalent to baseline levels (i.e. immediately prior to lens application in the morning) when the cornea is anesthetized. An equivalence margin of 10 points will be used.

Other Hypotheses
None.

3. TARGETED STUDY POPULATION

3.1. General Characteristics

Symptomatic contact lens wearers who report a CLDEQ-8 score of 20-37 will be recruited.

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 of legal age (18 years) and capacity of volunteer.
2. The subject must read, understand, and sign the STATEMENT OF INFORMED CONSENT and receive a fully executed copy of the form.
3. They must appear able and willing to adhere to the instructions set forth in this clinical protocol.
4. They have worn the same brand of soft spherical contact lenses for at least the previous three months, by self-report.
5. They are defined as 'symptomatic' contact lens wearers (CLDEQ-8 score of 20-37) with their habitual contact lenses.
6. They are willing to wear their lenses for approximately 14 hours on study days.
7. They have a wearable pair of spectacles, if applicable.
8. They agree not to participate in other clinical research for the duration of this study.

Inclusion Criteria after Baseline

9. They can attain high contrast logMAR visual acuity of 0.20 or better in their habitual contact lenses in each eye.

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. They are using any topical medication such as eye drops or ointment.
4. They have had cataract or corneal refractive surgery.
5. They are pregnant or breast-feeding by self-report.
6. They have any infectious disease (e.g. hepatitis) or any immunosuppressive disease (e.g. HIV), by self-report.
7. They have any known hypersensitivity or allergic reaction to any of the known ingredients in the anesthetic.
8. They have a history of severe allergic reaction or anaphylaxis.
9. They have a history of cardiac disease or hyperthyroidism.
10. They have taken part in any other contact lens or care solution clinical trial or research, within two weeks prior to starting this study.
11. They are an employee or immediate family member of an employee of clinical site (e.g., Investigator, Coordinator, Technician).

Exclusion Criteria after Baseline

12. They have any corneal distortion resulting from previous hard or rigid lens wear or have keratoconus.
13. They have grade 3 or greater of any of the following ocular surface signs which would contraindicate contact lens wear: corneal oedema, corneal vascularisation, corneal staining, tarsal conjunctival changes or any other abnormality which would normally contraindicate contact lens wear.

3.4. Enrollment Strategy

Study subjects will be recruited from the University of Manchester, UK'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

The study design is controlled, randomized, subject-masked, 3 treatment ×3 period, non-dispensing, contralateral study.

After a pre-screening assessment, eligible subjects will be invited to attend an initial visit. Subjects will be prescreened using the CLDEQ-8 questionnaire with their habitual lenses and those who are classified as symptomatic (CLDEQ-8 score of 20-37) will be scheduled for Visit 1.

At study Visit 1, subjects will be consented and screened for inclusion/exclusion criteria. If a subject is found to meet all eligibility criteria, they will be asked to attend Visit 2 which will take place on a different day. Subjects will be asked to wear their contact lenses early in the morning (at home) on the day of Visit 2 and to rate subjective comfort on a paper VAS scale immediately prior to lens application and 5 minutes post-application. They will be asked to attend the study visit having worn their habitual lenses for 14 ± 2 hours. At Visit 2, one of three areas (upper lid margin, lower lid margin or cornea) will be anesthetized on one eye, whilst the fellow eye will receive a saline placebo treatment in the same location. The ocular surface region and treatment will be randomly assigned. The right eye will always be assessed first. Subjective comfort scores (VAS scale) will be collected prior to and following the treatment on each eye (5 and 10 minutes post-treatment). On the day of corneal treatment, VAS comfort scores will also be collected immediately after lens removal prior to treatment application. Subjects will be asked to return for Visit 3 on a different study day, again having worn their lenses for 14 ± 2 hours and the same procedures as at Visit 2 will take place. The same procedures as for Visit 3 will be repeated for Visit 4. Visits 2-4 will be scheduled 1-14 days apart.

4.2. Study Design Rationale

Crossover designs are a well-established cost-effective study design in which subjects are exposed to multiple treatments during different time periods. The study design allows for a direct and meaningful comparison of three anesthesia treatments. A minimum period of 24 hours between visits (i.e. between each treatment) was implemented to reduce any potential carry-over effect that may bias the results.

4.3. Enrollment Target and Study Duration

A total of up to 20 subjects will be enrolled (informed consent signed) at a single clinical site (University of Manchester) in the UK, with a target of 15 to complete.

Subjects will be considered to be enrolled onto the study when they have signed the informed consent. A replacement subject will be enrolled if a subject discontinues from the study before completing the study visits.

Each subject will attend for four visits of up to 1 hour in duration. The study is expected to last approximately 5 months and include a 1-month enrollment period.

5. TEST ARTICLE ALLOCATION AND MASKING

5.1. Test Article Allocation

An ocular surface region (upper lid margin, lower lid margin or cornea) will be randomly allocated to each visit and a treatment (anesthesia or placebo) will be randomly allocated to each eye using a randomization scheme supplied by the study biostatistician. A single ocular region will be investigated at each visit and a single treatment will be applied to each eye at each visit. The clinical site will follow the randomization scheme provided and will complete enrollment according to the randomization list and will not pre-select or assign subjects. The assignment of the subjects must be performed at Visit 1. The following must have occurred prior to randomization:

- Informed consent has been obtained
- Subject meets all the inclusion / exclusion criteria
- Subject history and baseline information has been collected

The randomization scheme will be generated using the PROC PLAN procedure from the SAS Software Version 9.4 or higher (SAS Institute, Cary, NC).

The regions (upper lid margin, lower lid margin, or cornea) will be treated in a bilateral and random fashion using a Williams design with 3 regions and 3 periods. Each subject will be randomly assigned to one of six unique sequences (U/L/C, L/C/U, C/U/L, C/L/U, U/C/L, L/U/C). For each region within a sequence, the two treatments will be randomly assigned to the left and right eye (anesthesia left eye/placebo right eye or placebo left eye/anesthesia left eye).

5.2. Masking

This is a single masked study, where subjects will be unaware of the treatment (anesthesia or placebo) applied to each eye, since the Investigator will be preparing the treatment out of sight of the subject. Investigators and clinical site personnel involved in the data collection will not be masked as to the identity of the treatment.

5.3. Procedures for Maintaining and Breaking the Masking

Study codes will not be used for masking.

6. STUDY INTERVENTION

6.1. Identity of Test Articles

None.

6.2. Ancillary Supplies/Products

Table 1: Ancillary Supplies

Solution Name/Description	Proxymetacaine hydrochloride 0.5% (local anesthetic)	0.9% w/v sodium chloride solution
Manufacturer	Chauvin Pharmaceuticals Ltd (a subsidiary of Bausch + Lomb)	Crest Medical Ltd (or alternative sponsor-approved product)
Preservative	None	None
Other distinguishing items (dye, packaging, approval status, etc.	Single-use minims (0.5ml)	Single-use pods (20ml)

6.3. Administration of Test Articles

Not applicable.

6.4. Packaging and Labeling

Not applicable.

6.5. Storage Conditions

Not applicable.

6.6. Collection and Storage of Samples

No samples will be collected as part of the study procedures.

6.7. Accountability of Test Articles

Not applicable. Subjects will be using their habitual lenses.

7. STUDY EVALUATIONS

7.1. Time and Event Schedule

Table 2: Time and Events

Visit Information	Visit 0 Pre-screen	Visit 1 Screening and Baseline	Visit 2 Treatment region 1	Visit 3 Treatment region 2	Visit 4 Treatment region 3, Final Evaluation
Time Point		24 hours to 28 days from Visit 0	24 hours to 14 days from Visit 1	24 hours to 14 days from Visit 2	24 hours to 14 days from Visit 3
Estimated Visit Duration		45 minutes	1 hour	1 hour	1 hour
Phone/electronic consent	x				
Statement of Informed Consent		x			
Demographics		x			
Medical History/Concomitant Medications		x			
Habitual Contact Lens Information		x			
Inclusion/Exclusion Criteria		x			
Changes in concomitant medications, medical history and adverse events			x	x	x
CLDEQ-8 Questionnaire	x				
Len Application (prior & 5 min post) VAS			x	x	x
Entrance Visual Acuity		x	x	x	x
Slit Lamp Biomicroscopy		x	x	x	x
Eligibility	x	x			
Randomization		x			
Lens wear information			x	x	x
Patient reported ocular symptoms			x	x	x
Lens Fit Assessment			x	x	x
Pre-treatment VAS comfort score			x	x	x
Application of topical anesthetic/saline			x	x	x

Visit Information	Visit 0 Pre-screen	Visit 1 Screening and Baseline	Visit 2 Treatment region 1	Visit 3 Treatment region 2	Visit 4 Treatment region 3, Final Evaluation
Time Point		24 hours to 28 days from Visit 0	24 hours to 14 days from Visit 1	24 hours to 14 days from Visit 2	24 hours to 14 days from Visit 3
Estimated Visit Duration		45 minutes	1 hour	1 hour	1 hour
Post-treatment VAS comfort score			x	x	x
Contact lens removal			x	x	x
Slit Lamp Biomicroscopy			x	x	x
Exit Visual Acuity		x	x	x	x
Study Completion					x

7.2. Detailed Study Procedures

VISIT 0

Visit 0: Pre-Screening			
Step	Procedure	Details	[redacted]
0.1	Phone/electronic Consent	Obtain Consent from the subject utilizing an EC-approved consent for use of CLDEQ-8 in the study	
0.2	Pre-screen CLDEQ-8 Questionnaire	The subject will respond to the CLDEQ-8 • If CLDEQ-8 sum score is equal or greater than 20, then schedule Visit 1 for screening • If CLDEQ-8 sum score is lower than 20, subject is not eligible for further screening	

VISIT 1

Subjects should be asked to attend Visit 1 wearing their habitual contact lenses. Subjects should bring some confirmation of their lens type (e.g. lens box, blister, etc.) if this information has not already been provided.

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	Informed Consent

		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 date of birth, 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	CLDEQ-8 Questionnaire	The Investigator will enter the subject's responses to the Pre-screen CLDEQ-8 Questionnaire on the database.	[redacted]
1.6	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.	

Visit 1: Baseline			
Step	Procedure	Details	[redacted]
1.7	Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD and OS) with their habitual contact lenses in place. *(Inclusion criterion: LogMAR of 0.20 or better in both eyes)*	Eurolens Research SOP # 12a
1.8	Slit Lamp Biomicroscopy	Efron Slit Lamp Classification Scale will be used to grade the findings and determine eligibility. If there are any Grade 3 or higher slit lamp finding, the subject is ineligible to continue at this time, but may return up to one additional time to determine eligibility. If discontinued a final examination must be completed. If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	Eurolens Research SOP #13
1.9	Eligibility after Baseline	All responses to Inclusion Criteria questions must be answered "yes" and all responses to Exclusion Criteria questions must be	

Visit 1: Baseline			
Step	Procedure	Details	[redacted]
		answered "no" for the subject to be considered eligible.	
1.10	VAS scale dispensing	Subjects will be issued with VAS scales to record subjective comfort on the days of Visit 2-4. Subjects will receive instructions for completion.	Appendix E
1.11	Exit VA	Record subjects' distance high contrast visual acuity to the nearest letter (OD and OS) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP # 12a
1.12	Randomization	Subjects will be assigned a line on the randomization scheme.	
1.13	End of Visit 1	Subject discharged and asked to return for Visit 2. Subjects can leave wearing contact lenses, spectacles or unaided as determined by the investigator.	

VISITS 2 - 4

Subject should attend Visits 2-4 having worn their habitual contact lenses for 14 ± 2 hours having had a washout period of 1 – 14 days from the previous visit.

Pre-Visit 2-4 (at home)			
Step	Procedure	Details	[redacted]
2.1	Subjective comfort	Subjective comfort scores (vertical VAS scale) will be collected for each eye immediately prior to lens application. A text message will be sent the day before to remind subjects to complete the VAS scales immediately prior to and 5 minutes after lens application	[redacted]
2.2	Lens application	Subjects will apply their habitual contact lenses. The time of lens application will be recorded on the VAS scale. A text message will be sent to subjects to confirm lens application. Subjects will be asked to reply 'yes' if they have applied the contact lenses or 'no' if they have not. If they have not applied, the visit can be rescheduled to a different day for a maximum of two further occasions.	
2.3	Subjective comfort	Subjective comfort scores (vertical VAS scale) will be collected for each eye after 5 minutes of lens settling.	[redacted]

Visit 2-4 (in clinic after 14 ± 2 hours of lens wear)			
Step	Procedure	Details	[redacted]
2.4	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.	
2.5	Wearing Time	Record the wearing time since application and comfortable wearing time.	
2.6	Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	[redacted]
2.7	Collection of VAS scale	The investigator will collect the comfort VAS scales and will enter the scores on the database. If subjects have not completed the VAS scales, the visit can be rescheduled to a different day for a maximum of two further occasions.	
2.8	Entrance Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD and OS) with their habitual contact lenses.	Eurolens Research SOP #12a
2.9	Slit Lamp Biomicroscopy (white light only)	Efron Slit Lamp Classification Scale will be used to grade the findings. If any of these slit lamp findings are Grade 3 or higher, it will be recorded as an Adverse Event.	Eurolens Research SOP #13
2.10	Subjective Lens Fit Assessment	Lens fit will be recorded according to a -2 to +2 integer scale for each of the following criteria: Horizontal centration: -2 = Extremely Nasal -1 = Slightly Nasal 0 = Optimum +1 = Slightly Temporal +2 = Extremely Temporal Vertical centration: -2 = Extremely Superior -1 = Slightly Superior 0 = Optimum +1 = Slightly Inferior +2 = Extremely Inferior Coverage: -2 = Extremely Inadequate -1 = Slightly Inadequate 0 = Optimum	

		+1 = Slightly Excessive +2 = Extremely Excessive Movement -2 = Extremely Inadequate -1 = Slightly Inadequate 0 = Optimum +1 = Slightly Excessive +2 = Extremely Excessive	
2.11	Subjective comfort	Subjective comfort scores (vertical VAS scale) will be collected for each eye.	[redacted]
2.12	Right eye Application of topical treatment	One ocular region (upper lid margin, lower lid margin or cornea) of the right eye will be anesthetized or will receive a saline placebo treatment, based on the randomization scheme. The procedures will take place with the subject's lenses in situ when the lid margins are treated. When the cornea is anesthetized, the subject's habitual lens will be removed and immediately dosed with the anesthetic as outlined in SOP #54. The lens will not be spun to removed excess liquid and will not be soaked in any solution prior to re-insertion. The dosing/re-application procedure should take place as quickly as possible to avoid the lens from dehydrating excessively. If any problems with the application of the treatment occur, subjects are eligible to repeat the visit on another day only once.	Eurolens Research SOP #54
2.13	Right eye Subjective comfort	Subjective comfort scores (vertical VAS scale) will be collected for the right eye after 5 and 10 minutes post-treatment. For the cornea, the contact lens is removed and then reapplied as part of the treatment application procedures. Comfort scores will also be collected immediately (ideally within 30 seconds) after lens removal prior to treatment application.	[redacted]
2.14	Left eye Application of topical treatment	The same ocular region (upper lid margin, lower lid margin or cornea) of the left eye will be anesthetized or will receive a saline placebo treatment, based on the randomization scheme.	Eurolens Research SOP #54

		The procedures will take place with the subject's lenses in situ when the lid margins are treated. When the cornea is anesthetized, the subject's habitual lens will be removed and immediately dosed with the anesthetic as outlined in SOP #54. The lens will not be spun to removed excess liquid and will not be soaked in any solution prior to re-insertion. The dosing/re-application procedure should take place as quickly as possible to avoid the lens from dehydrating excessively. If any problems with the application of the treatment occur, subjects are eligible to repeat the visit on another day only once.	
2.15	Left Subjective comfort	Subjective comfort scores (vertical VAS scale) will be collected for the left eye after 5 and 10 minutes post-treatment. For the cornea, the contact lens is removed and then reapplied as part of the treatment application procedures. Comfort scores will also be collected immediately (ideally within 30 seconds) after lens removal prior to treatment application.	[redacted]
2.16	Contact lens removal	Contact lenses will be removed and discarded.	
2.17	Exit Slit Lamp Biomicroscopy (Visits 2-3 only)	Efron Slit Lamp Classification Scale will be used to grade the findings. Adverse events shall be documented and followed to resolution. If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	Eurolens Research SOP #13
2.18	Exit VA (Visits 2-3 only)	Record subjects' distance high contrast visual acuity to the nearest letter (OD and OS) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP # 12a
2.19	End of Visit (Visits 2-3)	Subject discharged and asked to return for next visit. Subjects can leave wearing spectacles or unaided as determined by the investigator.	

FINAL EVALUATION

The final evaluation will ordinarily 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	Efron Slit Lamp Classification Scale will be used to grade the findings. Adverse events shall be documented and followed to resolution. If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	Eurolens Research SOP #13
F.3	Exit Visual Acuity	Record subjects' distance visual acuity to the nearest letter (OD and OS) with their habitual spectacle correction in place (or unaided if applicable).	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 (when applicable)

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	Slit Lamp Biomicroscopy	Efron Slit Lamp Classification Scale will be used to grade the findings. If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops may be instilled.	Eurolens Research SOP # 13
U.4	Exit Visual Acuity	Record the exit distance visual acuity to the nearest letter (OD and OS) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP # 12a

7.4. Laboratory Procedures

Not applicable.

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 study visits
- have not withdrawn/discontinued from the study for any reason described in Section 8.2

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 in the opinion of the Principal Investigator
- 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 contact lens wear
- 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 two study visits
- Subject not compliant with lens wear schedule

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

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 or therapies for this study include: any topical medication such as eye drops or ointment or any medications that in the opinion of the investigator would 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 study procedures. 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 [redacted]

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.

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. At the Investigator's discretion, the study participant may be followed by the Investigator through delivery. However, this data will not be collected as part of the clinical study database. 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.

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 (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 if applicable 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.

This is a feasibility study and further exploratory analysis can be undertaken if necessary at the discretion of the study responsible clinician.

14.2. Sample Size Justification

The plan is to enroll 20 subjects with a target of 15 subjects to complete the study. This is a pilot study and the sample size was not based on any empirical power calculation.
The tables below, provided using the POWER procedure in SAS 9.4, summarizes statistical power based on the following assumptions:

- Testing for superiority with 0 VAS points and equivalence with +/- 10 VAS points
- True difference for superiority: 5, 7.5, 10 points and for equivalence: -5, 0, -5 points
- Estimated standard deviations of 15 and 20 points
- Intraclass correlations of 0.4, 0.6, and 0.8
- Two-sided type I error rate of 0.05
- 15 subjects successfully complete the study

Table 3: Power Analysis for the Primary Hypothesis (Superiority)

		Intraclass Correlation		
Difference (Test-Control)	Estimated Standard Deviation	0.4	0.6	0.8
5.0	15	0.300	0.393	0.617
5.0	20	0.211	0.269	0.425
7.5	15	0.515	0.661	0.897
7.5	20	0.351	0.460	0.705
10.0	15	0.724	0.864	0.987
10.0	20	0.515	0.661	0.897

The study is appropriately powered (power above 80%) to show superiority of anesthetized eyes over eyes that received the placebo when the difference in VAS comfort is at least 7.5 points and the intraclass correlation is at least 0.8.

Table 4: Power Analysis for the Primary Hypothesis (Equivalence)

		Intraclass Correlation		
Difference (Test-Control)	Estimated Standard Deviation	0.4	0.6	0.8
-5.0	15	0.259	0.386	0.617
-5.0	20	0.081	0.202	0.422
0.0	15	0.453	0.728	0.974

		Intraclass Correlation		
Difference (Test-Control)	Estimated Standard Deviation	0.4	0.6	0.8
0.0	20	0.117	0.334	0.794
5.0	15	0.259	0.386	0.617
5.0	20	0.081	0.202	0.422

The study is appropriately powered (power above 80%) to show equivalence between comfort scores at post-treatment and 5-minute post-application when there is no difference (0 VAS points) and the intraclass correlation is at least 0.8.

14.3. Analysis Populations

Safety Population:
All subjects that complete any study procedures after signing the Informed Consent form (subjects will be wearing their habitual contact lenses in this study). 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

All planned analysis for this study will be conducted with an overall type I error rate of 5%.

14.5. Primary Analysis

VAS Comfort

VAS Comfort score at 5 and 10 minutes post treatment will be analyzed separately using a linear mixed model. The model will include the following experimental design factors: treatment, sequence of treatment, region, sequence of region, period, time event, and first-order carryover as fixed effects. Baseline characteristics such as age and gender may be included as covariates when appropriate. The covariance between residual errors for the same subject across periods will be modeled using one of the following covariance structures: Compound Symmetry (CS) or Unstructured (UN). The covariance structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fits the data. The Kenward and Roger method[8] will be used for the calculation of denominator degrees of freedom.

The null and alternative hypothesis for superiority of anesthetized eyes compared to eyes that received the placebo with respect to VAS comfort at post treatment, where $\mu_A - \mu_P$ is the difference in VAS comfort between anesthesia and placebo treatments, is as follows:

$$H_0: \mu_A - \mu_P \leq 0$$
$$H_A: \mu_A - \mu_P > 0$$

The hypothesis will be tested via corresponding two-sided 95% confidence interval for least-squares mean difference (anesthesia minus placebo) of VAS comfort. Superiority will be concluded if the lower limit is greater than 0 for at least one of the three ocular regions (upper lid margin, lower lid margin, or cornea).

The null and alternative hypothesis for equivalence of VAS comfort scores at post-treatment and 5-minutes post-application, where $\mu_1 - \mu_2$ is the difference in VAS comfort score between post-treatment and 5-minutes post-application, is as follows:

$$H_0: |\mu_1 - \mu_2| \geq 10$$
$$H_A: |\mu_1 - \mu_2| < 10$$

The hypothesis will be tested via corresponding two-sided 95% confidence interval for least-squares mean difference (post treatment minus post application) in VAS comfort score. Equivalence will be concluded if the upper limit is less than 10 and the lower limit is greater than -10.

VAS Comfort (Change)

VAS Comfort score change from pre-treatment to 5 and 10 minute post-treatment values will be analyzed separately using a linear mixed model. The model will include the following experimental design factors: treatment, sequence of treatment, region, sequence of region, period, and first-order carryover as fixed effects; subject as a random effect. Baseline characteristics such as age and gender may be included as covariates when appropriate. The covariance between residual errors for the same subject across periods will be modeled using one of the following covariance structures: Compound Symmetry (CS) or Unstructured (UN). The covariance structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fits the data. The Kenward and Roger method[8] will be used for the calculation of denominator degrees of freedom.

The null and alternative hypothesis for superiority of anesthetized eyes compared to eyes that received the placebo with respect to VAS comfort change from pre-treatment, where $\Delta_A - \Delta_P$ is the difference in VAS comfort change from pre-treatment between anesthesia and placebo treatments, is as follows:

$$H_0: \Delta_A - \Delta_P \leq 0$$
$$H_A: \Delta_A - \Delta_P > 0$$

The hypothesis will be tested via corresponding two-sided 95% confidence interval for least-squares mean difference (anesthesia minus placebo) of VAS comfort change from pre-treatment. Superiority will be concluded if the lower limit is greater than 0 for at least one of the three ocular regions (upper lid margin, lower lid margin, or cornea).

14.6. Secondary Analysis

VAS Comfort

The null and alternative hypothesis for superiority of eyes with the cornea anesthetized compared to with upper or lower lid margin anesthetized with respect to VAS comfort at post treatment, where $\mu_C - \mu_L$ is the difference in VAS comfort between cornea and either lower or upper lid margins, is as follows:

$$H_0: \mu_C - \mu_L \leq 0$$
$$H_A: \mu_C - \mu_L > 0$$

The hypothesis will be tested via corresponding two-sided 95% confidence interval for least-squares mean difference (cornea minus upper or lower lid margin) of VAS comfort. Superiority will be concluded if the lower limit is greater than 0 for at least one of the two differences (cornea minus upper lid margin or cornea minus lower lid margin).

The null and alternative hypothesis for equivalence of VAS comfort scores at lens removal and prior to lens application, where $\mu_1 - \mu_2$ is the difference in VAS comfort score between lens removal and prior to lens application, is as follows:

$$H_0: |\mu_1 - \mu_2| \geq 10$$
$$H_A: |\mu_1 - \mu_2| < 10$$

The hypothesis will be tested via corresponding two-sided 95% confidence interval for least-squares mean difference (lens removal minus prior to lens application) in VAS comfort score. Equivalence will be concluded if the upper limit is less than δ and the lower limit is greater than -10.

VAS Comfort (Change)

The null and alternative hypothesis for superiority of eyes with the cornea anesthetized compared to with upper or lower lid margin anesthetized with respect to VAS comfort change from pre-treatment, where $\Delta_C - \Delta_L$ is the difference in VAS comfort change from pre-treatment between cornea and either lower or upper lid margins, is as follows:

$$H_0: \Delta_C - \Delta_L \leq 0$$
$$H_A: \Delta_C - \Delta_L > 0$$

The hypothesis will be tested via corresponding two-sided 95% confidence interval for least-squares mean difference (cornea minus upper or lower lid margin) of VAS comfort change

from pre-treatment. Superiority will be concluded if the lower limit is greater than 0 for at least one of the two differences (cornea minus upper lid margin or cornea minus lower lid margin).

14.7. Other Exploratory Analyses

Not applicable.

14.8. Interim Analysis

No interim analysis is planned.

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.

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.

External Date Sources for this study include: Not Applicable

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
- 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 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[5] 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

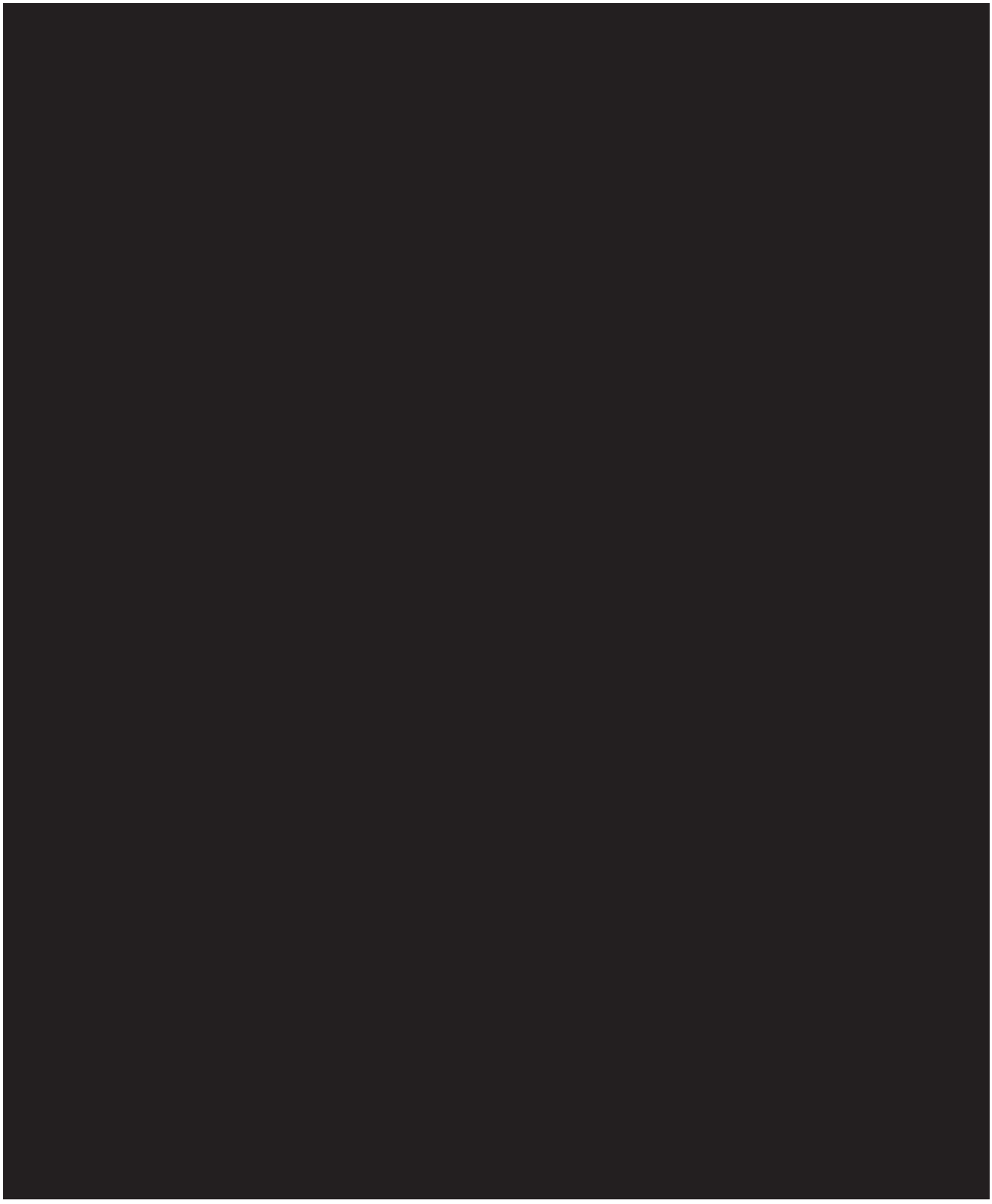
21. PUBLICATION

This study will be registered on ClinicalTrials.gov.

22. REFERENCES

1. ISO 14155:2011: Clinical Investigation of Medical Devices for Human Subjects — Good Clinical Practice. Retrieved September 12, 2018, from https://www.iso.org/standard/45557.html
2. International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP). Retrieved September 12, 2018, from http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
3. Declaration of Helsinki - Ethical principles for Medical Research Involving Human Subjects. Retrieved September 12, 2018, from 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). Retrieved September 12, 2018, from https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
5. General Data Protection Regulation. Retrieved September 12, 2018, from http://www.eugdpr.org/
6. Navascues-Cornago M. Clinical Study Report [redacted] June 27, 2018.
7. Navascues-Cornago M, Maldonado-Codina C and Morgan PB. Effect of selective topical anesthesia on initial comfort of rigid contact lenses. British Contact Lens Association 39th Annual Clinical Conference and Exhibition. May 29-31, 2015, ACC, Liverpool, UK.
8. Kenward, M. G., and Roger, J. H. Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood.Biometrics; 1997, 53:983–997.

APPENDIX A: PATIENT REPORTED OUTCOMES (STUDY QUESTIONNAIRES)



[redacted]

APPENDIX B: PATIENT INSTRUCTION GUIDE

Not Applicable - study will use habitual contact lenses only.

APPENDIX C: PACKAGE INSERT (APPROVED PRODUCT)

1. Minims Proxymetacaine hydrochloride 0.5% (Chauvin Pharmaceuticals Ltd)
2. Sterile Saline Pod Material Safety Data Sheet (Crest Medical Ltd)

Art.76559 GB255E01-05.07
9335200

Minims®

Proxymetacaine hydrochloride 0.5% Eye Drops

0.5% w/v Proxymetacaine Hydrochloride BP

About Minims Proxymetacaine hydrochloride 0.5%

The name of this medicine is Minims Proxymetacaine hydrochloride 0.5%. Each Minims unit is a sterile, single-use eye drops container which contains 0.5% w/v proxymetacaine hydrochloride solution. The solution also contains purified water and small amounts of hydrochloric acid and sodium hydroxide. Each Minims unit contains approximately 0.5ml of solution. Each carton contains 20 Minims units. Proxymetacaine hydrochloride is used as a local anaesthetic.

Who makes Minims Proxymetacaine hydrochloride 0.5%?

Minims Proxymetacaine hydrochloride 0.5% is manufactured by Laboratoire Chauvin S.A. Z.I. Ripotier, 07200/Aubenas, France. The Marketing Authorisations for Minims Proxymetacaine hydrochloride 0.5% (PL 0033/0151 & PA 118/46/1) are held by Chauvin Pharmaceuticals Ltd, 106 London Road, Kingston-Upon-Thames KT2 6TN, England.

What is it for ?

Minims Proxymetacaine hydrochloride 0.5% is used to numb the eye temporarily. This could be necssary for a number of reasons. Most often, Minims Proxymetacaine hydrochloride 0.5% is used to allow your doctor or eye specialist to measure the pressure inside your eye or perform minor operations such as the removal of stitches and foreign bodies. This product is not intended to be used as a long term treatment for painful eye conditions.

Before using Minims Proxymetacaine hydrochloride 0.5%

- Are you allergic to Proxymetacaine hydrochloride?
- Do you suffer from heart disease?
- Do you have an overactive thyroid gland?

If the answer to any of these questions is yes, tell your doctor or eye specialist before you use this product.

When your eye has been numbed it is important not to rub it and to keep it free of dust and bacteria. Your doctor or eye specialist will make sure that your eye is properly protected.

If you are pregnant (or if you think that you might be pregnant) you should tell your doctor or eye specialist before Minims Proxymetacaine hydrochloride 0.5% is used. It is possible that you still receive it, but it is also possible that an alternative may be used.

Proxymetacaine hydrochloride is more comfortable for your eyes than some local anaesthetics but you may still feel some stinging when the drops are first added. Your sight may also become blurred for a short time.

Make sure that you do not try to drive or use machinery until your sight has returned to normal.

Some eye examinations involve the use of staining solutions as well as local anaesthetics. Proxymetacaine hydrochloride should not be given at the same time as a particular stain called fluorescein. Your doctor or eye specialist will be aware of this and will make sure that a long enough time interval is allowed between the addition of Minims Proxymetacaine hydrochloride 0.5% and fluorescein solution.

The solution should be colourless or pale yellow. Minims Proxymetacaine hydrochloride 0.5% should not be used if it is darker than pale yellow in colour.

This product should not be used in premature babies.

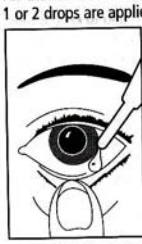
Art.76559 GB255E01-05.07
9335200

Using Minims Proxymetacaine hydrochloride 0.5%

The amount of anaesthetic used will vary, depending on the procedure which is to be carried out:

For measuring the pressure inside your eye, or for the removal of foreign bodies, 1 or 2 drops just before the procedure is sufficient.

For the removal of stitches, 1 or 2 drops are applied 2 to 3 minutes before operating.



If deep or prolonged anaesthesia is needed, 1 drop can be applied every 5 to 10 minutes. This can be repeated up to 7 times.

The doctor or eye specialist will put the drops in your eye for you. You may be asked to press on the inner corners of your eyes for a minute to prevent the solution draining into your nose and throat. Your eye will remain numb for between 15 minutes and 1 hour, depending on how many drops you received. Avoid touching the eye until the anaesthetic has worn off.

The Minims unit should be discarded after use.

Local anaesthetic eye drops can damage the surface of the eye if they are used too much of too often. Your doctor or eye specialist will make sure that this does not happen.

It is very unlikely that you will suffer an overdose from Minims Proxymetacaine hydrochloride 0.5%, but if you suddenly feel unwell after receiving the drops, tell your doctor or eye specialist.

After using Minims Proxymetacaine hydrochloride 0.5%

Minims Proxymetacaine hydrochloride 0.5% does not usually cause unwanted side effects, but allergic reactions have occasionally occurred. These can affect the cornea (a transparent membrane covering the iris and pupil of the eye) and the iris. Your doctor or eye specialist will be able to tell if an allergic reaction occurs. Other reactions such as widening of the pupil, temporary paralysis of the lens or irritation of the conjunctiva (a mucous membrane which lines the inside of the eyelid) are very rare and will quickly wear off. If you do suddenly feel uncomfortable or unwell after receiving Minims Proxymetacaine hydrochloride 0.5%, you should tell your doctor or eye specialist.

Storing Minims Proxymetacaine hydrochloride 0.5%

- Minims Proxymetacaine hydrochloride 0.5% should be stored in a refrigerator at 2-8°C. Do not allow it to freeze. The solution should not be used if it is more than pale yellow in colour.
- The expiry date for Minims Proxymetacaine hydrochloride 0.5% stored in a refrigerator at 2-8°C is printed on each Minims unit overwrap and on the carton label. Do not use it after this date.
- If necessary, the product may be stored at temperature not exceeding 25°C for up to 1 month only, in which case a label bearing the relevant expiry date will be affixed to the carton label.

This leaflet applies only to Minims Proxymetacaine hydrochloride 0.5%, but it does not contain all the information known about it. If you have any questions or are not sure about anything, ask a doctor, eye specialist or pharmacist.

Date of (Partial) Revision of Text:
September 2007.

Bausch & Lomb
Laboratoire Chauvin
Chauvin Pharmaceuticals Ltd.,
London Road,
Kingston-Upon-Thames
KT2 6TN, England.
Tel : 020 8781 2900
Fax : 020 8781 2901

MATERIAL SAFETY DATA SHEET
Sterile Saline Pod

Reviewed 29/12/2012

1. Identification of the Substance/Preparation and the Company

Trade Name:	Sterile Saline Pod
Product Code:	7912 20ml pods of Sterile Sodium Chloride
Use of the preparation:	A liquid for eye and wound irrigation
Company:	Crest Medical Ltd Healthcare Enterprise House 17 Chesford Grange Woolston Warrington, WA1 4RQ, UK
Contact:	Tel: +44 (0) 845 230 2092 Fax: +44 (0) 845 230 2091 Email: sales@crestmedical.co.uk www.crestmedical.co.uk

2. Hazard Identification

This preparation is, according to the conventional method of Directive 1999/45/EC and subsequent amendments, classified as not "Hazardous".

3. Composition/information on ingredients

CAS No: Not applicable, preparation is a mixture.
EINECS No: Not applicable, preparation is a mixture.

Composition: An aqueous solution containing 0.9% w/v sodium chloride EP.

4. First Aid Measures

Based on the composition of this preparation none would be required.

5. Fire Fighting Measures

Only the packaging containing the preparation would burn.

Suitable extinguishing media: Water spray/fog, foam, carbon dioxide and dry powder.

Standard protective equipment should be worn by fire-fighters.

In the event of a large fire toxic fumes containing oxides of carbon may be formed, which would necessitate the use of a self-contained breathing apparatus.

6. Accidental Release Measures

Personal precautions: None required.

Methods for cleaning-up: Mechanically collect any packaging for subsequent disposal and then rinse any spilled preparation to a drain with water.

7. Handling and Storage

Handling: No special measures required.

Storage: Store under normal warehouse conditions.

8. Exposure Controls/Personal Protection

Exposure controls: No assigned values for the ingredients of this preparation.

Personal protection: None required.

9. Physical and Chemical Properties

Appearance: Preparation is a clear colourless liquid
Odour: Preparation is odourless
pH of preparation: 4.5 – 7.0
Boiling point of preparation: ca 100°C
Flash point of preparation: N/A
Flammability: Preparation is non flammable
Solubility: Preparation is completely miscible with water

10. Stability and Reactivity

This preparation is stable under normal conditions of storage/use and no chemical incompatibility is known.

11. Toxicological Information

Crest Medical Limited 17 Chesford [redacted] Warrington. WA1 4RQ
Head office 01925 898 200 Fax 01925 898 270 Email www.crestmedical co uk
Registered Office: 17 Chesford Grange, Woolston, Warrington, WA1 4RQ, United Kingdom
Registered in England No. 03876927 VAT Reg. No.:GB927193604

Based on the ingredients present and their concentrations this preparation is, according to the conventional method of Directive 1999/45 EC and subsequent amendments, classified as not "Dangerous" according to health criteria.

12. Ecological Information

Based on the ingredients present and their concentrations this preparation is, according to the conventional method of Directive 1999/45 EC and subsequent amendments, classified as not "Dangerous" to the environment.

13. Disposal Considerations

Dispose of the packaging according to local and national regulations whilst the preparation can be discharged to any drain.

14. Transport Information

This preparation is classified as not "Hazardous" for transport purposes

ADR – Not regulated

IMDG – Not regulated

IATA – Not regulated

15. Regulatory Information

This preparation is not classified as not "Hazardous" for labeling purposes.

Label for supply:

Active Ingredient	0.9% w/v sodium chloride EP
Safety phrase	For external use only

Directions for Use:

Take Pod from box and remove 1 ampoule.

To open: Take ampoule upright and open it by twisting off the top.

How to use: For directional irrigation position the ampoule and squeeze firmly, taking care not to touch the nozzle.

Crest Medical Limited 17 Chesford [redacted] Warrington. WA1 4RQ
Head office 01925 898 200 Fax 01925 898 278 Email www.crestmedical co uk
Registered Office: 17 Chesford Grange, Woolston, Warrington, WA1 4RQ, United Kingdom
Registered in England No. 03876927 VAT Reg. No.:GB927193604

Discard any unused solution.

16. Other Information

This Safety Data Sheet, which takes into consideration the requirements of Directive 1999/45/EC plus subsequent amendments, has been prepared in accordance with Regulation (EC) No 1272/2008 as amended by Regulation (EC) No 453/2010. It is believed to be correct and corresponds to the latest state of scientific/technical knowledge but all data, instructions, recommendations and/or suggestions are made without guarantee.

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Head office 01925 898 200 Fax 01925 898 270 Web www.crestmedical co uk
Registered Office: 17 Chesford Grange, Woolston, Warrington, WA1 4RQ, United Kingdom
Registered in England No. 03876927 VAT Reg. No.:GB927193604

APPENDIX D: [redacted]

- [redacted] Subject Reported Ocular Symptoms
- [redacted] Patient Reported Outcomes
- Eurolens Research SOP #13: Examination of the anterior segment using slit lamp biomicroscopy. Version 4, Feb 5, 2018.
- Eurolens Research SOP #12a: The set-up, measurement of visual acuity and procedures for carrying out an over-refraction using the Eurolens computerized LogMAR VA chart. Version 2, Dec 19, 2017.
- Eurolens Research SOP #54: Procedure for selectively anesthetising the cornea and eyelid margins. Version 1, June 1, 2017.

[redacted] SUBJECT REPORTED OCULAR SYSTEMS

[redacted]

Subject Reported Ocular Symptoms/Problems

OVERVIEW

This document contains instructions for the determination of whether or not ocular symptoms and problems are present. If present, this document can be used to determine the characterization of the level and/or frequency of such symptoms or problems.

MATERIALS

The appropriate Case Report Form Module

PROCEDURE

The following steps are used in the patient workup and recording of reported symptoms or problems.

Step	Action
1	Following the instruction in the appropriate Case Report Form Module, ask the subject if he/she has experienced any eye symptoms or problems with lens wear or study lenses. Read the questions provided in the appropriate Case Report Form Module to the subject.
2	If no symptoms or problems are reported by the subject for one or both eyes, check the "No" box(es).
3	If one or more symptoms or problems are reported by the subject for one or both eyes, check the "Yes" box(es).
4	The investigator or assistant will ask the subject to characterize each reported symptom or problem according to the scale provided in the module.

GRADING SCALE

Refer to the appropriate Case Report Form Module.

ADDITIONAL INFORMATION

Questions to subject should be modified to reflect time period of assessment and whether habitual or study lenses are being assessed.

TRAINING REQUIREMENTS

The training requirement for this document is "Read Only."

[redacted] PATIENT REPORTED OUTCOMES

[redacted] Patient Reported Outcomes

OVERVIEW

This document contains instructions for the collection of patient reported outcomes. A patient reported outcome (PRO) is an umbrella term that covers a whole range of potential types of measurement but is used specifically to refer to self-reports by the patient in a clinical study. The objective of a PRO is to quantify subjective responses.

MATERIALS

Case report form modules (developed by the clinical lead and PRO lead).

PROCEDURE

Specific instructions will be given to the investigator for all questionnaires used in a study.

GRADING SCALE

The grading scale will be specific to each questionnaire used.

ADDITIONAL INFORMATION

All questionnaires as defined by the current revision of **VCCL-0034** must be requested through the PRO lead.

REFERENCES

- FDA Guidance For Industry – Patient Reported Outcome Measures: Usein Medical Product Development to Support Labeling Claims. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- Current revision of **VCCL-0034**.

TRAINING REQUIRE-MENTS

The training requirement for this document is “Read Only.”

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.

THE SET-UP, MEASUREMENT OF VISUAL ACUITY AND PROCEDURES FOR CARRYING OUT AN OVER-REFRACTION USING THE EUROLENS COMPUTERIZED 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

First issued: v0; July 8, 2009
Reviewed (with changes): v1; February 7, 2014
Reviewed (no changes): v1; February 2, 2016
Reviewed (with changes): v2; December 19, 2017

Document control

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Document type:	Clinical standard operating procedure
Number of pages:	11

Document author: _____ Date: 19 Dec 2017
Neil Chatterjee,
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Document reviewed by: _____ Date: 19 Dec 2017
Gillian Howarth,
Research Optometrist

Document reviewed and approved by: _____ Date: 22 Dec 2017
Michelle Inwood,
Project Officer

Document approved by: _____ Date: 12-Jan-2018
Philip Morgan,
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**).

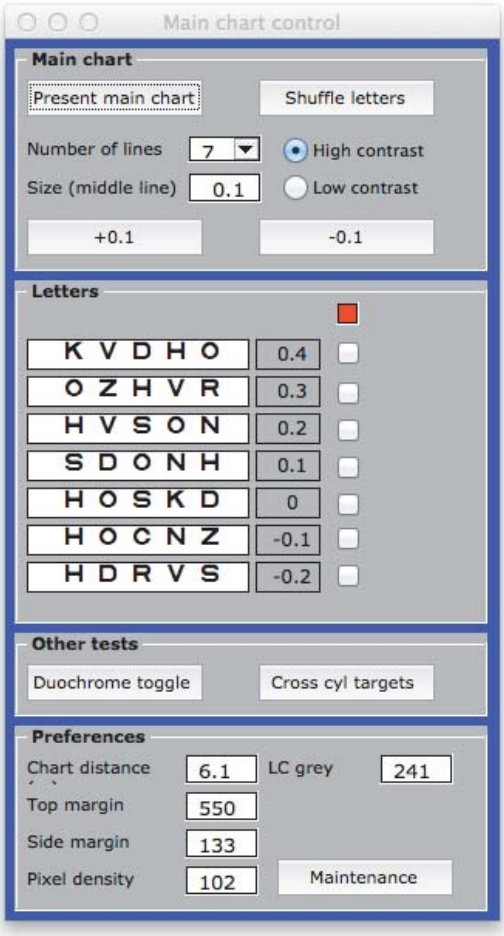


Figure 1. Chart control panel

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.

PROCEDURE FOR SELECTIVELY ANESTHETISING THE CORNEA AND EYELID MARGINS

Eurolens Research

Clinical
Standard Operating Procedure

Procedure for selectively anaesthetising the cornea and eyelid margins

Associate Director
Carole Maldonado-Codina

First issued: v0; October 20, 2015
Current revision: v0; October 20, 2015
Reviewed (with changes): v1; June 1, 2017

Document control

Title:	Procedure for selectively anaesthetising the cornea and eyelid margins
Document type:	Clinical standard operating procedure
Number of pages:	5

Document author: Carole Maldonado-Codina Date: 1 June 2017
Carole Maldonado-Codina
Associate Director

Document reviewed by: Maria Navascues-Cornago Date: 1 JUNE 2017
Maria Navascues-Cornago
Optometric Research Associate

Document reviewed and approved by: Michelle Inwood Date: June 1, 2017
Michelle Inwood
Project Officer (Business Systems)

Document approved by: P Morgan Date: 1 June 2017
Philip Morgan
Director

Summary

These guidelines describe how small quantities of topical anaesthetic can be used to selectively anaesthetise individual areas on the ocular surface.

Responsibilities

This procedure can be performed by clinical investigators.

List of equipment

Proxymetacaine hydrochloride 0.5% (Chauvin Pharmaceuticals Ltd)
Cotton bud
Eyelid retractor (Eyegenie™, Wilson Ophthalmic Corp.) (optional)
Any soft contact lens

Procedure

This procedure can take place either for the cornea or the eyelid margins (upper and lower).

1. **Cornea**

   Two methods for anaesthetising the cornea can be used:

   a. 'Contact lens' method:

      i. A soft contact lens is removed from its blister packaging and placed into a lens holder (from a barrel contact lens case) and centrifuged for 2 seconds using a custom low-speed centrifuge to remove surface packaging solution from the contact lens surface.
      ii. A 10 µl drop of anaesthetic is dispensed onto the back surface of the contact lens using an automated micropipette and a sterile pipette tip.
      iii. The subject is asked to face downwards.
      iv. The upper and lower eyelids are retracted using fingers or an Eyegenie (Eyelid retractor).
      v. The investigator applies the dosed contact lens directly onto the cornea, whilst the eyelids are held apart for a further minute to allow the anaesthetic to be absorbed and avoid spreading to other parts of the ocular surface.

vi. The contact lens is removed, the eyelids are then released and the subject is allowed to blink normally.

b. 'Drop' method:

i. The subject is asked to lift the chin and lean the head backward during the procedure.

ii. The upper and lower eyelids are retracted using fingers or an Eyegenie (Eyelid retractor).

iii. A 3µl drop of anaesthetic is dispensed onto the central cornea using an automated micropipette and a sterile pipette tip. Flexible silicone tubing will be attached to the pipette tip.

iv. The eyelids are held apart for a minute to allow the anaesthetic to be absorbed and avoid spreading to other parts of the ocular surface.

v. The eyelids are then released and the subject is allowed to blink normally.

2. Eyelid margins

This procedure can be carried out on the upper and lower eyelid margins.

a. A soft contact lens is applied to the eye to shield the cornea.

b. A cotton bud is manipulated until a fine thread is created at the tip.

c. This tip is saturated with the anaesthetic.

d. The saturated cotton bud tip is then used to 'brush' the full length of the upper or lower lid margin for 30 seconds.

e. The upper lid margin should be completely everted whilst the lower lid margin needs only to be partially everted.

f. The eyelid is kept fully or partially everted (whichever is relevant) for 30 seconds.

g. A second application of anaesthetic using the saturated cotton bud is performed for 30 seconds.

h. The eyelid is kept fully or partially everted (whichever is relevant) for a further minute to allow the anaesthetic to be absorbed and avoid spreading to other parts of the ocular surface.

i. The contact lens is removed, the eyelids are then released and the subject is allowed to blink normally

The anaesthetic effect lasts between 15 minutes and one hour. The subject should be advised not to wear their own contact lenses for at least two hours after the procedure..

Appendix A

Minims Proxymetacaine hydrochloride 0.5% Eye Drops – Chauvin Pharmaceuticals Ltd (Patient Information Leaflet)

- Proxymetacaine hydrochloride 0.5% will be stored as indicated: at 2° to 8° C, refrigerated (not frozen).

APPENDIX E: VAS SCALE

Subject Number: ☐ ☐ ☐ Date: _____ / _____ / _____

Pre-Visit 2: Before Lens Application

To the right are lines with markers.

The top marker on each line means the best comfort imaginable.

The bottom marker means the worst comfort imaginable.

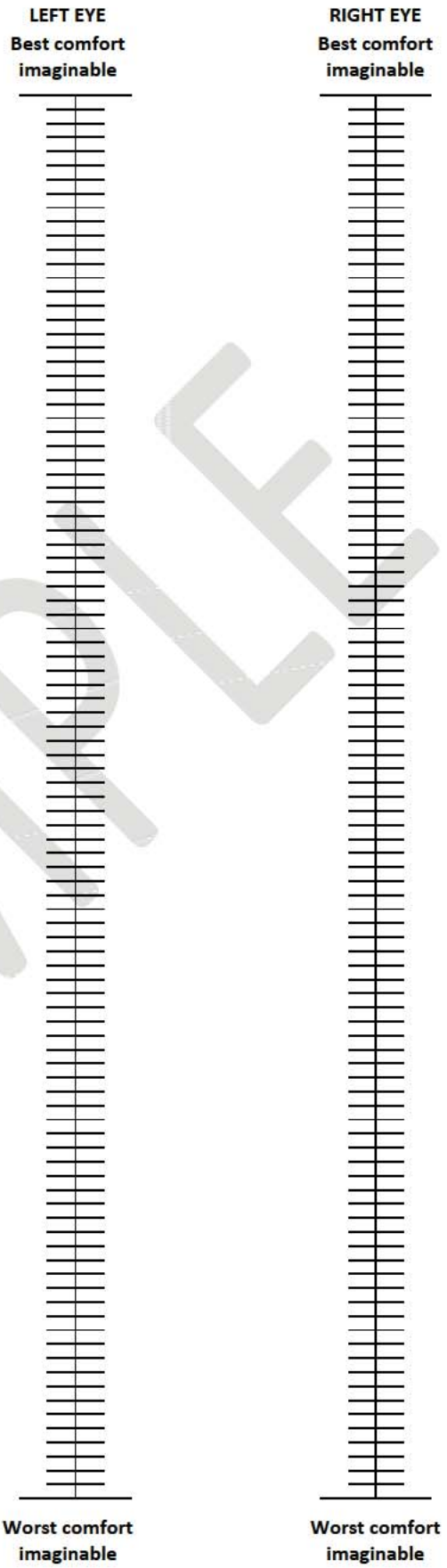
CAREFULLY think about each eye. Please take your time and mark your responses as accurately as possible.

Draw an X on the line to rate <u>how comfortable each EYE is overall</u> on the scale (left eye and right eye).

Subject Initials	**Today's Date**	**Time**

Investigator Use Only:

OD Value	**Site Initials**	**Date**
OS Value	**Site Initials**	**Date**



PROTOCOL COMPLIANCE INVESTIGATOR(S) SIGNATURE PAGE

Protocol Number and Title: CR-6292 An investigation of the impact of localized topical anesthesia of the ocular surface on end-of-day contact lens discomfort

Version and Date: 1.0 24 September 2018

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.

Principal Investigator:

_____ _____
Signature Date

_____
Name and Professional Position (Printed)

Institution/Site: _____
Institution/Site Name

_____
Institution/Site Address