Clinical investigation plan

C17-614 (EX-MKTG-85)

A fitting evaluation of hydrogel and silicone hydrogel spherical contact lenses

A clinical evaluation for
CooperVision Inc.

Study Leader
[redacted]

Principal Investigator
[redacted]

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Document control

Study title:	A fitting evaluation of hydrogel and silicone hydrogel contact lenses (C17-614) (EX-MKTG-85)
Sponsor company:	CooperVision Inc.
Document type:	Clinical investigation plan.

Study summary

This double-masked, randomised, bilateral crossover non-dispensing study will compare the clinical performance and subjective acceptance of the NewDay, Biomedics 1-day and Proclear 1-day daily disposable soft contact lenses.

Forty subjects will be enrolled on this study and will wear each lens type for approximately one hour on three separate study days in random sequence. The following will be assessed throughout the study: ocular physiology, lens fit, visual acuity, and subjective response.

A study summary is shown in Table 1.

Visit	Procedures
Information and consent presentation	Short on-line presentation of study aims and procedures
Visit 1	Informed consent taken Explanation of study procedures and subject instructions Medical, ocular and contact lens history Refraction Auto-keratometry Biomicroscopy Fitting of lens pair 1 Visual acuity Subjective scores Lens fit
Visit 2	Subjective scores Visual acuity Lens fit Biomicroscopy
Visit 3	Medical and ocular history Biomicroscopy Fitting of study lens pair 2 Visual acuity Subjective scores Lens fit
Visit 4	Subjective scores Visual acuity Lens fit Biomicroscopy
Visit 5	Medical and ocular history Biomicroscopy Fitting of study lens pair 3 Visual acuity Subjective scores Lens fit
Visit 6	Subjective scores Visual acuity Lens fit Biomicroscopy Exit form signed and payment issued

Table 1: Study summary.

Section 1. Overview

1.1 Background

This project seeks to compare the short-term clinical performance of the NewDay, Biomedics 1-day and Proclear 1-day (all CooperVision Inc.) daily disposable soft contact lenses.

1.2 Personnel

This work will be conducted at Eurolens Research, The University of Manchester under the general direction of Philip Morgan PhD MCOptom FAAO FBCLA. The Principal Investigator for the work is Carole Maldonado-Codina PhD MCOptom FAAO FBCLA.

1.3 Study objectives

This study aims to compare the short-term clinical performance of the three contact lenses.

1.4 Study design

This will be a randomised, double-masked, crossover, bilateral non-dispensing study, controlled by cross-comparison. Forty subjects will wear each lens brand for approximately one hour, on three separate study days in random order. Lenses will only be worn during study visits.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that high contrast visual acuity in the lenses will be substantially equivalent.

Visual acuity assessment, biomicroscopy, lens surface data and subjective responses will generate data that are likely to be continuous and normally distributed. As such, these will be compared using linear regression models or other parametric methods. Subjective preferences will be compared using chi-squared tests. Lens fit data are expected to be ordinal data and assessed with non-parametric approaches. Deviations from this statistical plan will be discussed in the final report. Deviations may be necessary due to differences between the actual data distribution compared with the anticipated data distribution.

1.5.1 Power analysis

Assessment using a dataset from a similar, previous study found that a power of 0.89 or greater is provided by 35 completing subjects to detect a 0.05 difference in high contrast visual acuity. This analysis assumes a two-tailed paired analysis and an alpha of 0.05. To allow for discontinuations, 40 subjects will be recruited.

1.6 Risk analysis

This study is considered to be a non-significant risk study based on United State Food and Drug administration (FDA) and International Standards Organization (ISO) guidelines due to the daily wear nature of the study. With the potential benefit of this study, the work is considered to be ethically justifiable. Ethical approval will be sought from the University of Manchester Senate Committee on the Ethics of Research on Human Beings (hereafter referred to as Manchester UREC). The work where practical will be conducted in accordance with the ICH Good Clinical Practice Guidelines and the international standard BS EN ISO 14155:2011 'Clinical investigation of medical devices for human subjects'.

Section 2. Resources

2.1 Subject selection

In this work 40 subjects will be recruited and enrolled.

2.1.1 Subject withdrawal and replacement

This study includes six clinical visits. Once the study consent form is signed, the subject is considered to be enrolled on the study. Subjects who have signed the consent form, but who have not completed the first study visit will usually be replaced. All subject data will be included in the final analyses unless there are strong grounds for exclusion; such grounds will be detailed in the final report. At the end the study, all subjects will sign a study exit form.

2.1.2 Subject recruitment

Subjects will be recruited by one or more of following means:

1. Posting study details on The University of Manchester's 'Research Volunteers' website.
2. Correspondence to existing wearers on the Eurolens Research database of subjects.
3. Advertising through a variety of media via a format separately approved by Manchester UREC.

2.1.3 Inclusion criteria

Subjects will only be eligible for the study if:

1. They are of aged 18-40 and have capacity to volunteer.
2. They understand their rights as a research subject and are willing and able to sign a Statement of Informed Consent.
3. They are willing and able to follow the protocol.
4. They agree not to participate in other clinical research for the duration of this study.
5. They have a contact lens spherical prescription between -1.00 to - 6.00D (inclusive)
6. They have a spectacle cylindrical correction of -0.75D or less in each eye (based on the ocular refraction).
7. They can attain at least 0.10 logMAR distance high contrast visual acuity in each eye with the study lenses within the available power range.
8. They currently use soft contact lenses or have done so in the previous six months.

2.1.4 Exclusion criteria

Subjects will not be eligible to take part in the study if:

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 surgery.
5. They have had corneal refractive surgery.
6. They have any corneal distortion resulting from previous hard or rigid lens wear or have keratoconus.
7. They are pregnant or lactating.
8. They have any ocular abnormality which would, in the opinion of the investigator, normally contraindicate contact lens wear.
9. They have any infectious disease which would, in the opinion of the investigator, contraindicate contact lens wear or pose a risk to study personnel; or they have any immunosuppressive disease (e.g. HIV), or a history of anaphylaxis or severe allergic reaction.
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.

2.2 Subject discontinuation

In general, subjects should be discontinued at any time, if it is in their best interests, as judged by the investigator. Reasons for this may include clinical signs of grade 3 or more, lack of motivation, discomfort, repeated refusal to follow instructions or the use of non-study products such as solutions or lenses. Subjects will be discontinued if a serious adverse event occurs or if they miss two or more planned consecutive visits. Subjects who fail to satisfy all the inclusion and exclusion criteria will be discontinued and replaced. Subjects may choose to leave the study at their own request. All discontinuations will be carefully recorded.

2.3 Safety parameters, adverse events and concurrent illnesses

The key safety parameters are the serious and significant adverse events listed in Appendix A (adverse events are classified as 'serious', 'significant' or 'non-significant'). Clinical assessment is made at the study visit(s) for these parameters. The presence of any ocular adverse event will be reported on CVI report forms and those ocular adverse events described as 'serious' or 'significant' will be detailed in the final report. Similarly, any concurrent illness that is likely to impact on the relevance and quality of the captured data will be noted on the case report form.

2.3.1 Investigator obligations

At all times the investigator will act in the best interest of the subject. Referral or treatment of an adverse event or other clinical finding should be initiated in the best clinical judgement of the investigator, irrespective of the participation in the clinical study.

2.3.2 Reporting obligations

In the case of a 'serious' or 'significant' ocular adverse event, the Principal Investigator will notify the Industrial Contact Person as soon as possible. Manchester UREC and any regulatory authorities will be informed as required.

2.4 Study termination

If it becomes necessary to terminate the study earlier than planned, the Industrial Contact Person will notify the Principal Investigator who will end the study with the cooperation of other staff members. Manchester UREC will be informed.

2.5 Protocol deviations

Any deviations from this protocol will be recorded, and reported to the Industrial Contact Person as appropriate. Manchester UREC will be informed as necessary.

2.5.1 Protocol amendments

Any amendments will be agreed between the Industrial Contact Person and the Principal Investigator with the cooperation of other staff members. Amendments will be recorded, identified and distributed. Approval from Manchester UREC will be obtained as necessary.

2.6 Study resources

Study products will be stored according to the manufacturer's product instructions.

2.6.1 Lenses

Details of the study lens are provided in Table 2. All lens types are CE marked. Initial lens selection will be as indicated by the manufacturer fitting guidelines.

	Lens A	Lens B	Lens C
Name	NewDay	Biomedics 1-Day	Proclear 1-Day
Manufacturer	CooperVision	CooperVision	CooperVision
Material	Methafilcon A IV	Ocufilcon B	Omafilcon A
EWC (%)	58%	52%	60%
BOZR (mm)	8.7	8.7	8.7
Diameter (mm)	14.3	14.2	14.2
Spherical powers (D)	-0.25 to -6.00 (0.25 steps)	-0.25 to -6.00 (0.25 steps)	-0.25 to -6.00 (0.25 steps)

Table 2: Study lenses.

2.6.1.1 Use of lenses

Lenses will be worn by the subjects in the clinic only.

2.6.2 Care regimen

No care system will be used on this study.

2.6.3 Inventory control

All study lenses lenses will be provided by CooperVision Inc.

All worn lenses will be discarded. Unworn lenses will be returned to:

Jose Vega
Sr. Manager Global Medical Scientific Affairs
CooperVision Inc.
6150 Stoneridge Mall Rd
Suite 370
Pleasanton
CA 94588

2.6.4 Clinical equipment

Clinical equipment is regularly maintained and calibrated as required. Standard operating procedures and international standards are used where appropriate.

2.7 Study control

This study is controlled by cross-comparison. Bias will be minimised by randomising the order of assessment. Subjects and investigators will be masked to the three lenses - lenses will be over-labelled. Masking may be 'broken' if deemed necessary, by the Principal Investigator or Industrial Contact Person.

2.8 Documentation

Documents related to this work that require archiving will be kept by Eurolens Research for a period of 10 years after completion of the final report. The Sponsor's permission will be sought before the documents are destroyed.

2.9 Data collection and analysis

Data collected in this work will be recorded on a custom developed database and an established data trail. Data handling will include export of the study information from the clinical database into spreadsheet format for manipulation, followed by export into a statistical package for analysis. Most clinical data will be entered directly onto the electronic case report form and is considered to be source data.

2.10 Study completion

The clinical phase of the study will be considered as complete when all subjects have signed the exit statement.

2.11 Confidentiality

All matters related to this work will remain confidential within Eurolens Research, the funding company and any regulatory authority (e.g. Manchester UREC). Eurolens Research will take all reasonable steps to ensure that specific lens-related information is not passed on to study participants unless this is required for clinical management of an adverse event. Personal subject information will not be made available. To cater for this, subjects will only be referred by their unique identity number in the study report. The data activities of Eurolens Research are registered with the data protection officer at The University of Manchester.

2.12 Study monitoring

In order to provide quality control and quality assurance as part of this work, the study monitor will:

1. Liaise closely with the Principal Investigator.
2. Monitor and ensure the safety of the subjects.
3. Ensure that the investigation is being conducted according to the protocol.
4. Monitor and review (or oversee review of) the study records to ensure accuracy.
5. Document their observations and make them available to relevant authorised parties (e.g. Manchester UREC).
6. Implement the Eurolens Research clinical monitoring standard operating procedure.

Section 3. Subject management

3.1 Visit scheduling

Subjects will be required to attend two visits (approximately one hour apart) on each of three separate days, a minimum of 24 hours apart.

3.1.1 Unscheduled visits

Subjects who attend at their own volition, (or as instructed to do so by the investigator) rather than for a scheduled study visit, will be examined and the visit will be classified as 'unscheduled'. Data collected at these visits will be recorded on the clinical study database.

3.1.2 Missed visits

Subjects not attending for a visit will be contacted and encouraged to return for assessment. If two consecutive study visits are missed, the subject will be discontinued. It is expected that Eurolens Research personnel will attempt all reasonable means of communication in this event, including corresponding with the subject by letter.

3.2 Visit conduct

3.2.1 Pre-enrolment

The subject will receive a study-specific information form outlining the study at least 24 hours before the initial visit

At a suitable time, each subject will be asked to watch a short on-line information presentation detailing study visits and procedures. They will be asked to complete several multiple-choice questions to gauge their understanding of the study. Upon successful completion of these questions, the subject will be booked to attend the initial visit. Subjects should be asked not to wear their habitual contact lenses on the day of the study visit.

3.2.2 Visit 1

Subjects should attend this visit wearing their spectacles. They will then be required to sign an informed consent form prior to enrolment. A copy of the signed form will be issued to the subject. When the subject has signed the consent form, they are considered to be enrolled on the study.

Subjects will be instructed on the following:

1. Lens handling, application and removal, where necessary.

2. Specific study instructions, such as the importance of not using any other contact lens products.
3. General contact lens information such as the management of red eyes.

The following procedures will be performed (any ocular measurement procedures outlined below will be carried out on each eye):

1. Details of the ocular history and contact lens wearing history of the subject will be noted (including habitual lenses, modality, wear time and comfortable wear time).
2. Auto-keratometry measures will be recorded.
3. The investigator will perform refraction and distance monocular logMAR visual acuity (both high and low contrast), in accordance with the current Eurolens Research 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'.
4. Slit lamp biomicroscopy will be carried out for the signs outlined in Table 4 and in accordance with the current Eurolens Research Standard Operating Procedure 'Examination of the anterior segment using slit lamp biomicroscopy'. Grades will be scored to the nearest 0.1 unit in the best judgement of the investigator using Efron Grading Scales.

Classification	Primary signs	Secondary signs
Signs	Conjunctival redness Limbal redness Corneal neovascularisation Epithelial microcysts Corneal oedema Corneal staining Location of staining Conjunctival staining Conjunctival indentation 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 3: Biomicroscopic signs.

The presence of any ocular adverse events will be recorded (see Appendix A).

5. The investigator will confirm that the subject satisfies all the inclusion and exclusion criteria. Subjects who fail to meet all the criteria at this time will usually be discontinued and replaced.
6. The first randomised lens pair (Appendix B) will be fitted and allowed to settle for five minutes. Subjects will insert the study lenses themselves.

7. Monocular logMAR visual acuity (high contrast) will be recorded before performing an over-refraction, and then monocular and binocular logMAR visual acuity (high contrast only) will be carried out with the over-refraction in place, and in accordance with the current 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'.
8. If an over-refraction of ±0.50D or more is found, a second lens pair will be applied and Step 7 above will be repeated.
9. The subject will be asked to score the following with reference to appropriate visual analogue scales (0-100) (Appendix C):
    - Handling
    - Comfort
    - Burning/stinging
    - Distance vision

[redacted]

11. Lens fit will be assessed using the following evaluations: horizontal and vertical centration, corneal coverage and movement. Normally, for an acceptable fit, centration and movement will fall within currently accepted clinical criteria [between 1 and +1 on a -2 to +2 grading scale (Appendix C)]. If the lens is graded as 'unacceptable' (i.e. any of the grades are +2 or -2), the investigator should state why.
12. Lens tightness on push-up will be recorded using the grading scale in Appendix C.

[redacted]

14. The subject will be asked to return after the study lenses have been in situ for one hour.

3.2.3 Visit 2

After approximately one hour of lens wear, the subject will return to the clinic and the following assessments will be made:

1. Recording of any ocular symptoms, adverse events since lens application.
2. The subject will be asked to score the following scores with reference to appropriate visual analogue scales (0-100) (Appendix C):
    - Comfort
    - Burning/stinging
    - Distance vision
2. Monocular logMAR visual acuity (high contrast) will be recorded before performing an over-refraction, and then monocular and binocular logMAR visual acuity (high contrast only) will be carried out with the over-refraction in place, and in accordance with the current 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'.

[redacted]

15. Lens fit will be assessed using the following evaluations: horizontal and vertical centration, corneal coverage and movement. Normally, for an acceptable fit, centration and movement will fall within currently accepted clinical criteria [between 1 and +1 on a -2 to +2 grading scale (Appendix C)]. If the lens is graded as 'unacceptable' (i.e. any of the grades are +2 or -2), the investigator should state the reasons why.
4. Lens tightness on push-up will be recorded using the grading scale in Appendix C.

[redacted]

6. The subject will remove the lenses and will be asked to score the following with reference to appropriate visual analogue scales (0-100) (Appendix C):
    - Handling on removal
7. Slit lamp biomicroscopy will be performed as described in Section 3.2.2.

8. Subjects will be discharged and asked to attend the next study day without their habitual lenses in situ.

3.2.4 Visit 3

Subjects should attend this visit without their contact lenses in situ. The following will be carried out:

1. Recording of any ocular symptoms, adverse events and concomitant medications since the last visit.
2. Monocular logMAR visual acuity (high contrast) in each eye using the refraction result found in Section 3.2.2 in accordance with the current 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'.
3. Slit lamp biomicroscopy will be carried out for the signs outlined in Table 4 and in accordance with the current Eurolens Research Standard Operating Procedure 'Examination of the anterior segment using slit lamp biomicroscopy'. Grades will be scored to the nearest 0.1 unit in the best judgement of the investigator using Efron Grading Scales.

Classification	Primary signs	Secondary signs
Signs	Conjunctival redness Limbal redness Corneal neovascularisation Epithelial microcysts Corneal oedema Corneal staining Location of staining Conjunctival staining Conjunctival indentation 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 4: Biomicroscopic signs.

The presence of any ocular adverse events will be recorded (see Appendix A).

4. The second randomised lens pair (Appendix B) will be fitted and allowed to settle for five minutes. Subjects will insert the study lenses themselves.
5. Steps 7-14 in Section 3.2.2 will be repeated.

3.2.5 Visit 4

After approximately one hour of lens wear, the same procedures as Visit 2 will be performed.

3.2.6 Visit 5

Subjects should attend this visit without their contact lenses in situ. The same procedures as Visit 3 will be performed, with the third lens pair being applied.

3.2.7 Visit 6

After approximately one hour of lens wear, the same procedures as Visit 2 will be performed.

At the final visit (or when the subject is discontinued at an earlier visit) the subject will sign a study exit statement acknowledging that the work is complete, although they may have been asked by the investigator to attend a post-study follow-up visit, and that they should continue to use their lenses and solutions as advised, and seek aftercare for their contact lenses. A copy of this signed form will be issued to the subject.

The subject will be issued with their payment and discharged.

3.2.8 Post-study follow-up visit

In the case of a subject who exits the study with significant clinical signs or symptoms, the investigator must undertake to examine the subject at intervals he/she determines to be clinically appropriate until the sign or symptom has resolved or returned to a level that is considered to be clinically acceptable. Details from these visits will be recorded on a post-study follow-up visit form.

3.3 Monitoring subject compliance

Subjects are required to adhere to the instructions provided during this clinical investigation. This will be confirmed at the study visits by verbal questioning of the subject by the investigator.

3.4 Missing, unused and spurious data

The absence of any data will be carefully and critically considered. If appropriate, partial datasets will be included in the final analysis. Any data missing from a subject visit will be outlined in the report by indicating the number of subjects included for each analysis. Data that are unused or considered to be spurious will be detailed and discussed in the report.

Section 4. Study co-ordination

4.1 Document processing

All case report forms will be processed and evaluated by Eurolens Research, who will produce the final report with full statistical analysis. A draft report will be sent to the Industrial Contact Person in order to make comments and ask for re-drafts. If no comments are received from the Industrial Contact Person within eight weeks, a final report will be released with a separate document control page (in duplicate), requesting the Industrial Contact Person to sign both copies, one to keep and the other to be returned to Eurolens Research.

4.2 Disclosure

All matters relating to this clinical study are confidential and should only be disclosed to relevant authorised parties. More precise details relating to disclosure are outlined in the Research Agreement. None of the investigators involved in this work owns equity in the funding company.

4.3 Personnel

Principal Investigator

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Eurolens Research
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Pleasanton
CA 94588
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Appendix A

Adverse events

Classification	Definition
Serious Adverse Event	Those events that are life-threatening, or result in permanent impairment of a body function, or permanent damage to a body structure or necessitate medical (therapeutic) or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
Significant Adverse Event	Those non-serious adverse events that occur with contact lens usage that are not sight-threatening but are usually symptomatic and may warrant therapeutic management and /or temporary or permanent discontinuation of contact lens wear.
Non-Significant Adverse Events	Those less severe non-serious adverse events that occur with contact lens usage that are not sight-threatening, may or may not be symptomatic and may warrant palliative management, such as ocular lubricants or temporary interruption of contact lens wear.
Unanticipated Adverse Device Effect	Adverse events in a clinical trial that were not previously identified in the protocol in terms of nature, severity, or degree of incidence. An Unanticipated Serious Adverse Device Effect is an unanticipated adverse event that is serious in nature and caused by or associated with the device and is considered reportable.

Code	Condition	Reporting
Serious Adverse Events		
01	Presumed infectious keratitis or infectious corneal ulcer	Notify sponsor as soon as possible, **within 24 hours**; IRB reporting as per requirements
02	Permanent loss of ≥ 2 lines of best spectacle corrected visual acuity (BSCVA)	
03	Corneal injury that results in permanent opacification within central cornea (6mm)	
04	Uveitis or Iritis (e.g. presence of anterior segment inflammation as described in ISO 11980, Annex B)	
05	Endophthalmitis	
06	Hyphema	
07	Hypopyon	
08	Neovascularization within the central 6mm of cornea	
00	Other serious event	
Significant Adverse Events		
11	Peripheral (outside central 6mm), non-progressive, non-infectious ulcer	Notify sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
12	Symptomatic corneal infiltrative event	
13	Superior epithelial arcuate lesions (SEALs) involving epithelial split	
14	Corneal staining ≥ dense coalescent staining up to 2mm in diameter (e.g. moderate, ISO 11980 grade 3)	
15	Corneal neovascularization ≥ 1.0mm vessel penetration (e.g. ≥ ISO 111980 Grade 2), if 2 grade change from baseline	
16	Any temporary loss of ≥ 2 lines BSCVA for ≥ 2wks	
17	Any sign and/or symptom for which subject is administered therapeutic treatment or which necessitates discontinuation of lens wear for ≥ 2 weeks	
10	Other significant event	
Non-significant Adverse Events		
21	Conjunctivitis (bacterial, viral or allergic)	Notify sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
22	Papillary conjunctivitis if ≥ mild scattered papillae/follicles approximately 1mm in diameter (e.g. ISO 11890 Grade 2), if 2 grade change from baseline	
23	Asymptomatic corneal infiltrative events	
24	Any sign and/or symptom for which temporary lens discontinuation for > 1 day is recommended (if not already classified)	
20	Other sign and/or symptom warranting classification as a non-significant adverse event	

Normal or adaptive symptoms

Transient symptoms such as end-of-day dryness, lens awareness, itching or burning or other discomfort may occur with contact lens wear and may occasionally reduce wearing time. ***These are not reported as adverse events unless in the investigator's opinion they are unexpected in nature, severe or have a high rate of occurrence.***