Clinical investigation plan

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(EX-MKTG-108)

A clinical evaluation of two contact lenses used with three care systems

A clinical evaluation for
CooperVision Inc.

Principal Investigator
Philip Morgan

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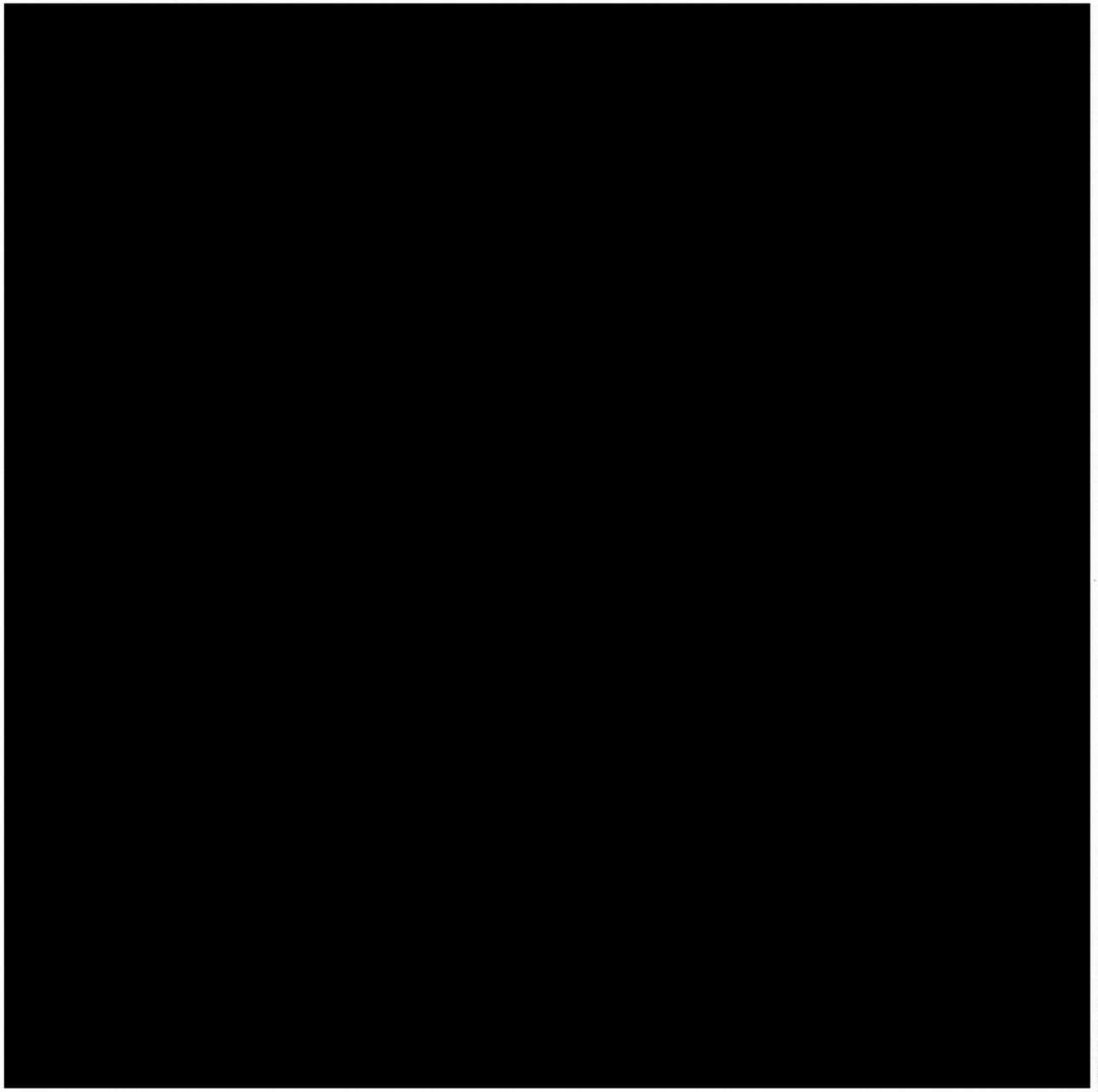
Contents



Study summary

This open-label, randomised, crossover study will compare the clinical performance and subjective acceptance of the two lens brands (Biofinity and Avaira Vitality) when used with three care systems (Hy-Care, All in One Light, and Refine One Step).

Thirty subjects will be enrolled on this study and will use each lens/solution combination in random sequence for one month each. The following will be assessed throughout the study: ocular physiology, [redacted] and subjective response.

A study summary is shown in Table 1.

Visit	Procedures
Information and consent presentation Initial visit	Short on-line presentation of study aims and procedures Informed consent taken Ocular and contact lens history Medical history Questions on contact lens/solution aftercare [redacted] Pre-corneal NIBUT [redacted] Fitting of first lens pair [redacted] Subjective scores Issue study lenses and first solution
1 month visit	Record wear times/medical/ocular history Retrieval of study products Subjective scores and questions [redacted] Fitting of second lens pair [redacted] Subjective scores Issue study lenses and second solution
2 month visit	Record wear times/medical/ocular history Retrieval of study products Subjective scores and questions [redacted] Fitting of third lens pair [redacted] Issue study lenses and third solution
3 month visit	Record wear times/medical/ocular history Retrieval of study products Subjective scores and questions [redacted] Fitting of fourth lens pair [redacted] Subjective scores Issue study lenses and fourth solution

4 month visit	Record wear times/medical/ocular history Retrieval of study products Subjective scores and questions [redacted] Fitting of fifth lens pair [redacted] Subjective scores Issue study lenses and fifth solution
5 month visit	Record wear times/medical/ocular history Retrieval of study products Subjective scores and questions [redacted] Fitting of sixth lens pair [redacted] Subjective scores Issue study lenses and sixth solution
6 month visit	Record wear times/medical/ocular history Retrieval of study products Subjective scores and questions Visual acuity [redacted] Exit form signed and payment issued

Table 1: Study summary.

Section 1. Overview

1.1 Background

The performance of different contact lens brands may vary when used with certain types of contact lens care systems. This includes the level of corneal staining seen at follow-up visits and may also include other measures of lens performance including subjective comfort and surface deposition. This project will evaluate two key CooperVision monthly replacement lens brands (Biofinity and Avaira Vitality) when used with three CooperVision care systems (Hy-Care, All in One Light, Refine One Step).

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 Philip Morgan.

1.3 Study objectives

This study aims to compare the clinical performance of the Biofinity and Avaira Vitality lenses when used in combination with three care systems (Hy-Care, All in One Light and Refine One Step).

1.4 Study design

This will be a randomised, open-label, crossover study, controlled by cross-comparison. Thirty subjects will use each lens and solution combination for a month in random sequence; that is for a total of six months. Follow-up visits for each lens will be performed after one month of wear. Lenses will be worn on a daily wear, reusable wear schedule.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is [redacted] subjective scores for the lenses will be substantially equivalent.

[redacted] 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

Using subjective comfort data from a previous, similar study, 22 subjects are required to complete the study for 80% power, assuming a difference of 10 points and a deviation of 16 points on a 0-100 scale. To allow for discontinuations, 30 subjects will be dispensed.

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 30 subjects will be recruited and enrolled.

2.1.1 Subject withdrawal and replacement

This study includes seven 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 dispensing 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 aged 18-50 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 are an existing wearer of reusable, single vision, spherical soft contact lenses.
5. They have a contact lens spherical prescription between -1.00 to - 6.50D (inclusive)
6. They have a spectacle cylindrical correction of -1.00D or less in each eye.
7. At dispensing, they can attain at least 0.20 logMAR distance high contrast visual acuity in each eye with the study lenses within the available power range.
8. They are willing to comply with the wear schedule (at least five days per week and for at least eight hours per day).
9. They agree not to participate in other clinical research for the duration of the study.

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 breastfeeding.
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 ocular adverse events listed in [redacted]

Clinical assessment is made at the study visit(s) for these parameters. The presence of any ocular adverse event will be reported on the case report forms and those 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' 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.

	Lens1	Lens 2
Name	Biofinity	Avaira Vitality
Manufacturer	CooperVision Inc	CooperVision Inc.
Material	Comfilcon A	Fanfilcon A
EWC (%)	48	55
BOZR (mm)	8.6	8.4
Diameter (mm)	14.0	14.2
Spherical powers (D)	-0.25 to -6.00 (0.50 steps)	-0.25 to -6.00 (0.50 steps)

Table 2: Study lenses.

2.6.1.1 Use of lenses

Both lens types will be worn on a daily wear, reusable basis (i.e. removed at end of day and stored in the relevant care system). Lenses should be worn for a minimum of eight hours per day, five days per week. The lenses are also to be worn for a minimum of two hours before attending the follow-up visits.

2.6.2 Care regimen

Details of the study solutions are provided in Table 3.

	Solution 1	Solution 2	Solution 3
Name	Hy-Care	All in One Light	Refine One Step
Manufacturer	CooperVision Inc.	CooperVision Inc.	CooperVision Inc.
Type	Multi-purpose	Multi-purpose	Hydrogen peroxide

Table 3: Study lenses.

2.6.3 Inventory control

All lenses and solutions will be supplied by CooperVision, Inc.

All worn lenses will be discarded. Unworn lenses will be destroyed.

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.

2.8 Documentation

Documents related to this work that require archiving will be kept by Eurolens Research for a period of 20 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 are 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). 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 seven visits – an initial dispensing visit and six follow-up visits, after one month of use of each lens/solution combination. [redacted]

[redacted]

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.

Should a subject attend for their initial visit and be ineligible for the study owing to a reason which the investigator believes to be transient (for instance slit lamp signs higher than those acceptable according to inclusion/exclusion criteria), a repeat first visit can be conducted a short time later. This visit may involve some or all of the scheduled initial visit procedures, with the exception of the consent process, which would not be repeated.

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 Initial visit

Prior to the dispensing visit, each subject will receive a study-specific information form outlining the study at least 24 hours before the consent visit and 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 Dispensing 1 visit. Subjects should attend this visit wearing their spectacles.

The subject, and will then be required to sign an informed consent form prior to enrolment [redacted] 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. Medical history will be recorded.
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]

8. [redacted]
9. [redacted]

Classification	Primary signs	Secondary signs
Signs	[redacted]	[redacted]
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 5: Biomicroscopic signs. Staining assessed with sodium fluorescein.

10. The presence of any adverse events will be recorded [redacted]
11. 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.
12. The first randomised lens pair will be fitted and allowed to settle for five minutes.
13. [redacted]
14. [redacted]
15. [redacted]
16. [redacted]

17. The subject will be asked to score the following subjective scores with reference to appropriate vertical visual analogue scales (0-100) [redacted]
    - Comfort
    - Vision
    - Burning/stinging
    - Overall score
18. The subject will be issued with a supply of contact lenses for the first study period, and with the first solution.
19. The subject will then be discharged and asked to return for the one-month follow-up visit [redacted]

3.2.2 One month visit

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

1. Any medical or ocular issues since the last visit will be recorded.
2. [redacted]
3. [redacted]
4. Retrieval of any unused lenses, plus solution and case.
5. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100) [redacted]
    - Comfort after insertion
    - Comfort before removal
    - Overall comfort
    - Vision
    - Variable vision
    - Vision at night
    - Dryness
    - Ocular redness
    - Burning/stinging
    - Ease of lens insertion
    - Ease of lens removal
    - [redacted]
    - [redacted]

- [redacted]

6. The presence of the following [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - Burning
   - [redacted]
   - Variable vision
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
7. [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]

[redacted]

9. [redacted]

[redacted]

11. [redacted]
12. [redacted]
13. The lenses will then be removed and discarded.
14. [redacted]
15. The same procedures as for the initial visit (3.2.1) points 6-15 will be carried out, with the second pair of lenses and second solution dispensed.

3.2.3 Two to five month visits

[redacted]

1. The same procedures as at the one month visit (3.2.2) will be carried out, with the next study lens and solution being fitted and dispensed in each case.

3.2.4 Six month visit

[redacted]

1. The same procedures as at the one month visit (3.2.2) will be carried out.
2. 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.
3. The subject will be issued with their payment and discharged.

3.2.5 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

[redacted]