Clinical investigation plan

C17-635 (EX-MKTG-95)

A clinical investigation of the short term clinical performance to a range of contact lenses and care system combinations

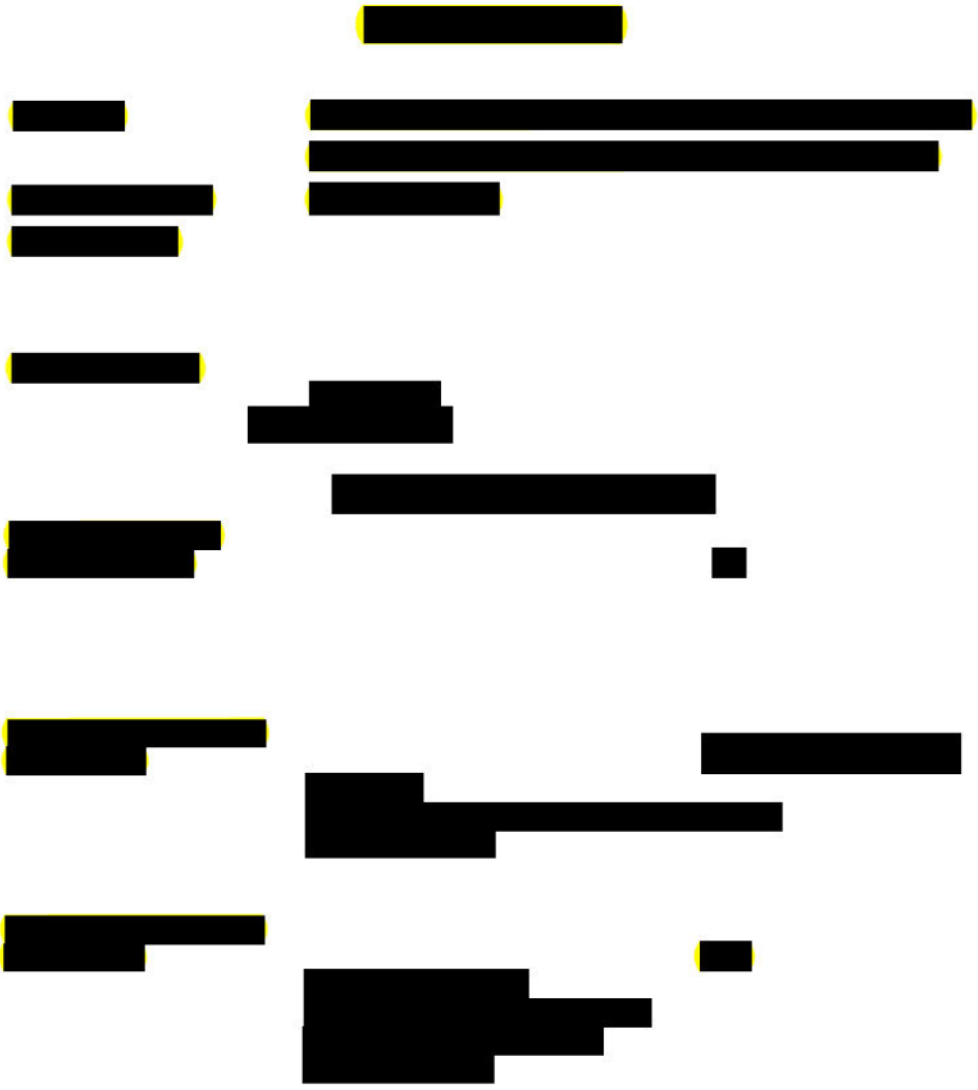
A clinical evaluation for
CooperVision Inc.

[redacted]

[redacted]

[redacted]

Contents



Study summary

This will be a randomised, double-masked, contralateral, cross-over study in which 28 subjects will wear the Avaira Vitality contact lens (fanfilcon A) and the Biofinity lens (comfilcon A), each lens having been soaked overnight in a lens care product ("solution"), Lite or Hy-Care. Follow-up visits will take place after approximately 2 hours of lens wear; with a two-day 'wash-out' period between the solutions. Key outcome measures for this study are a range of short term biomicroscopy signs. A study summary is shown in Table 1.

Visit	Procedures
1	Informed consent Explanation of study procedures and subject instructions Ocular and contact lens history Medical history [redacted] Biomicroscopy [redacted] Subjective scores
1b	[redacted] Subjective scores [redacted] Biomicroscopy
2	Biomicroscopy [redacted] Subjective scores
2b	[redacted] Subjective scores [redacted] Biomicroscopy Exit form signed and payment issued

Table 1: Study summary.

Section 1. Overview

1.1 Background

Various reports in the literature have reported significant levels of corneal staining with certain combinations of contact lens types and care systems. This phenomenon has been attributed to the binding of polyhexamethylene biguanide to lipids on the surface of a contact lens, and the subsequent release of the preservative at the ocular surface; although this theory has not been convincingly proven. The precise significance of such corneal staining is not generally agreed. This project seeks to examine the biomicroscopic response and other shortterm clinical responses after approximately two hours exposure to a range of contact lenses and solution combinations.

1.2 Personnel

This work will be conducted at Eurolens Research, The University of Manchester [redacted]

1.3 Study objectives

The objective of this study is to compare the short-term clinical response to all combinations of two lens types: Avaira Vitality and Biofinity with two care systems: Hy-Care and Lite.

The primary variables of interest are short-term biomicroscopy signs. Other variables of interest include subjective response [redacted].

1.4 Study design

This clinical study will be a randomised, double-masked, contralateral study, controlled by cross-comparison where the short term clinical response to each lens/care system combination will be assessed at a single study site. 28 subjects will wear lenses for approximately 2 hours on two days.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that biomicroscopy scores will not be different between the lens/solution combinations evaluated.

[redacted], biomicroscopy [redacted] 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.

[redacted]

[redacted] 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

The principal outcome variable to be tested in this work is corneal staining. If 22 subjects complete the work, the power of the study to detect a difference of 5 units for 'extent of corneal staining' on a 0-100 scale for corneal staining (assuming an alpha of 0.05, a two-tailed paired analysis and a standard deviation of intra-subject differences of 8 units) is 0.80. To cater for any subject discontinuations, 28 subjects will be recruited for the work.

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 28 subjects will be enrolled, with an aim to complete 22 subjects.

2.1.1 Subject withdrawal and replacement

This study includes four 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 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 of 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. Contacting volunteers on the Eurolens Research database of volunteers using email, phone and SMS.
2. Posting study details on The University of Manchester's 'Research Volunteers' website.
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 legal age (18) and 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 can be satisfactorily fitted with the study lens for a period of approximately 2 hours.
6. They can attain at least 0.20 logMAR distance high contrast visual acuity in each eye with their habitual spectacles.
7. They currently wear daily disposable soft contact lenses or have done so in the previous six months.
8. They are willing to comply with the wear schedule (approximately 2 hours on two different days)
9. They own a wearable pair of spectacles and agree to bring these to study visits.

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 currently wear reusable soft contact lenses in both eyes.
4. They are using any topical medication such as eye drops or ointment.
5. They have had cataract surgery.
6. They have had corneal refractive surgery.
7. They have any corneal distortion resulting from previous hard or rigid lens wear or have keratoconus.
8. They are pregnant or breast-feeding.
9. They have any ocular abnormality which would, in the opinion of the investigator, normally contraindicate contact lens wear.
10. They have Type 2 or greater corneal staining prior to lens application at Visit 1 or 2 [redacted]
11. They have corneal staining covering greater than 20% in any corneal region at Visit 1a or 2a [redacted]
12. 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.
13. 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 meet all the inclusion and exclusion criteria at this time will usually be discontinued and replaced. If in the opinion of the investigator, the subject may be eligible at a later date, the subject may be brought back for up to one repeat visit of this type. 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 [redacted] (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 noted on the eCRF and reported to the Sponsor using CVI report forms and those ocular adverse events described as 'serious' or 'significant' will be detailed in the final report. Similarly, any concurrent illness will be noted on the eCRF and comment added if is likely to impact on the relevance and quality of the captured data.

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

Non-significant ocular adverse events should be reported to the Industrial Contact Person within 5 working days. In the case of a 'serious' or 'significant' adverse ocular event, the Principal Investigator and the Industrial Contact Person will be notified within 24 hours. 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 on the eCRF, and reported to the Industrial Contact Person as appropriate. Manchester UREC will be informed as necessary. Device deficiencies will be recorded on the eCRF and reported to the Industrial Contact Person as appropriate.

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

2.6.1 Lenses

Details of the study lenses are provided in Table 2. All lens types are CE marked.

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

Table 2: Study lenses.

2.6.1.1 Use of lenses

Lenses will be worn for the short duration (approximately 2 hours) required in this study.

2.6.2 Care regimen

Details of the care regimens used in this study are provided in Table 3. All solutions are CE marked.

Name	Lite (US formulation)	Hy-Care (EU formulation)
Manufacturer	CooperVision Inc.	CooperVision Inc.
Active ingredients	Polyhexanide	Polyhexanide

Table 3: Care regimens.

2.6.2.1 Use of care regimen

Lenses will be removed from blister packaging and stored directly in solution for between 12 to 72 hours before being worn for approximately 2 hours by the subject. All lenses will be stored in generic contact lens cases supplied by the Sponsor. Contact lens cases will be pre-conditioned on arrival at the site prior to use on the study.

2.6.3 Randomization of lenses and care regimens

This is a double-masked (participant, investigator), contralateral, crossover study design. Lenses are worn as an unmatched pair. In order for subjects to use each possible combination of lens/solution, two dispensing visits will be required. The order of lens/solution use is detailed in the randomization schedule ([redacted] The randomization will be such that across the two study days, each eye will wear both of the study lenses. That is, if for the first solution the randomization determines that the right lens will wear the Avira Vitality lens and the left eye will wear the Biofinity lens, the laterality of the lenses will be swapped for the second solution.

2.6.4 Inventory control

All study lenses and study solutions will be supplied by CooperVision Inc. Worn lenses will usually be discarded, and any opened bottles of solution disposed of. Where possible, lenses associated with device deficiencies will be retained (stored in sterile saline), and returned to the Sponsor unless otherwise directed.

All unused materials will be returned to the Sponsor at the end of the study unless the site is otherwise directed by the Sponsor:

[redacted]

2.6.5 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 minimized by masking and randomizing the order of assessment. 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 (eCRF) 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 received* and/or signed the exit statement. (*In the event that a subject is lost to follow-up.)

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 authorized parties (e.g. Manchester UREC).
6. Implement the Eurolens Research clinical monitoring standard operating procedure.

2.13 Clinical trial registration

This study will be registered with clinicaltrials.gov in accordance with section 801 of the Food and Drug Administration (FDA) Act which mandates the registration of certain clinical trials of drugs and medical devices.

Section 3. Subject management

3.1 Visit scheduling

Subjects will be required to attend four visits across two different days.

Visit	Target	Allowable range
Visit 1	N/A	N/A
Visit 1b	2 hours after lens application	2-3 hours
Visit 2	2 days from Visit 1	2-14 days
Visit 2b	2 hours after lens application	2-3 hours

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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 Visit 1. Subjects will be asked not to wear their habitual contact lenses on the day of the study visit, and to attend wearing spectacles.

3.2.2 Visit 1

As instructed, subjects should attend this visit wearing their spectacles, having not worn their habitual contact lenses on the day of the visit. Subjects who have worn contact lenses will be asked to reschedule. Subjects 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:

[redacted]

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 [redacted]

[redacted] Details of the medical history, ocular history and contact lens wearing history of the subject will be noted [redacted]

[redacted] Slit lamp biomicroscopy will be carried out for the signs outlined in Table 5 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. Corneal staining will be graded for five regions [redacted]

Classification	Primary signs	Secondary signs
Signs	[redacted] Corneal staining Location of staining [redacted]	[redacted]
Scale	Efron Grading Scales (scored to nearest 0.1) Corneal staining (see [redacted]	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.

The presence of any ocular adverse events will be recorded, and reported as appropriate [redacted]

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. If in the opinion of the investigator, the subject may be eligible at a later date, the subject may be brought back for up to one repeat visit of this type, which may include some or all of the scheduled assessments. Informed consent will not be repeated.

6. Study lenses will be fitted according to the randomization table and allowed to settle for five minutes. Both investigator and subject are masked from the lenses and care system used, so the lenses will be provided in lens cases which do not detail lens or care system information. If a lens fails to settle within the first five minutes, eg excessive discomfort, or a suspicion that the lens is inverted, then the lens may be removed and a new lens reapplied.

[redacted]

10. The subject will be asked to score the following subjective scores, with reference to appropriate vertical analogue scales [redacted]
    - Comfort
    - [redacted]
    - Overall score
11. The subject will then be discharged and asked to return approximately 2 hours later.

3.2.3 Visit 1b (follow-up)

The following procedures will be performed:

1. The subject will be asked to score the following reactions:
    - Comfort before removal
    - Dryness
    - [redacted]
    - Overall score

[redacted]

[redacted]

5. The lenses will be removed and discarded.

[redacted]

7. A complete biomicroscopic examination will be conducted as outlined in Visit 1.
8. The subject will then be discharged and asked to return for Visit 2. Subjects are reminded to attend wearing spectacles, and not to wear habitual contact lenses on the day of the visit.

3.2.4 Visit 2

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

1. Medical and ocular history since the last visit will be recorded.

[redacted]

3. Slit lamp Biomicroscopy will be carried out for the signs outlined in Table 5 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. Corneal staining will be graded for five regions as described in [redacted]

Classification	Primary signs	Secondary signs
Signs	[redacted] Corneal staining Location of staining [redacted]	[redacted]
Scale	Efron Grading Scales (scored to nearest 0.1) Corneal staining (see [redacted]	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.

The presence of any ocular adverse events will be recorded, and reported as appropriate[redacted]

4. Subjects who have Type 2 or greater corneal staining and or corneal staining covering greater than 20% in any corneal region may be brought back for up to one repeat visit of this type, which may include some or all of the scheduled assessments.
5. Study lenses will be fitted according to the randomization table and allowed to settle for five minutes. Both investigator and subject are masked from the lenses and care system used, so the lenses will be provided in lens cases which do not detail lens or care system information. If a lens fails to settle within the first five minutes, e.g. excessive discomfort, or a suspicion that the lens is inverted, then the lens may be removed and a new lens reapplied.

[redacted]

8. The subject will be asked to score the following subjective scores, with reference to appropriate vertical analogue scales [redacted]:
   - Comfort

     [redacted]
   - Overall score

9. The subject will then be discharged and asked to return approximately 2 hours later.

3.2.5 Visit 2b (follow-up)

The following procedures will be performed:

1. The subject will be asked to score the following reactions:
    - Comfort before removal
    - Dryness
    - [redacted]
    - Overall score

[redacted]

6. The lenses will be removed and discarded.

[redacted]

8. A complete biomicroscopic examination will be conducted as outlined in Visit 1.
9. The subject will then be discharged and asked to return for Visit 2. Subjects are reminded to attend wearing spectacles, and not to wear habitual contact lenses on the day of the visit.

At the final visit (or when the subject is discontinued at an earlier visit) the subject will sign an 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.

3.2.6 Post-study follow-up visit

In the case of a subject who exits the study with significant ocular 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 authorized 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.