Clinical investigation plan

C21-706
(EX-MKTG-127)

Clinical evaluation of two silicone hydrogel contact lenses

A clinical evaluation for
CooperVision Inc.

Principal Investigator
Philip Morgan

September 2021

Contents

Study summary

This double-masked, randomised, bilateral crossover study will compare the short-term clinical performance and subjective acceptance of the Biofinity and Total30 soft contact lenses. Up to 38 subjects will be consented and will wear each lens brand for approximately six hours on separate study days, in random sequence. The following will be assessed throughout the study: [redacted] visual acuity and subjective response. [redacted]

A study summary is shown in Table 1.

V s t	Procedures
D spens ng 1	Informed consent taken Exp anat on of study procedures and subject nstruct ons Ocu ar, med ca and contact ens h stor es [redacted] v sua acu ty E g b ty F tt ng of study ens pa r 1 V sua acu ty [redacted] Subject ve scores Issue study enses
Fo ow-up 1 (after 6h of ens wear)	Rev ew med ca and ocu ar h stor es [redacted] V sua acu ty [redacted] V sua acu ty
D spens ng 2	Rev ew med ca and ocu ar h stor es [redacted] F tt ng of study ens pa r 2 V sua acu ty [redacted] Subject ve scores Issue study enses
Fo ow-up 2 (after 6h of ens wear)	Rev ew med ca and ocu ar h stor es Subject ve scores V sua acu ty [redacted] Removal of study enses [redacted] V sua acu ty Payment processed

Table 1: Study summary.

Section 1. Overview

1.1 Background

This project seeks to compare the short-term clinical performance of the Biofinity (CooperVision Inc.), and Total30 (Alcon Inc.) silicone hydrogel 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 Philip Morgan.

1.3 Study objectives

This study aims to compare the clinical performance of the Biofinity and Total30 contact lenses.

1.4 Study design

This will be a randomised, double-masked, crossover, bilateral study, controlled by cross-comparison. Up to 38 subjects will use each lens type for approximately six hours on separate study days, in random sequence.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that there is no difference for lens application scores for the two lens types.

Visual acuity assessment, [redacted] subjective responses [redacted] 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].

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 data from a previous study indicates that the standard deviation of intra-subject differences for lens application scores (0-100 scale) is 18 units. If a meaningful difference for lens application scores is 10 units, 36 completing subjects will provide 90% power assuming an alpha of 0.05 and a two-tailed analysis. To allow for discontinuations, 38 subjects will be recruited.

1.6 Risk analysis

This study is considered to be a non-significant risk study based on United States 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 14155:2020 'Clinical investigation of medical devices for human subjects - Good clinical practice'.

1.7 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 2. Resources

2.1 Subject selection

In this work, up to 38 subjects will be consented with the aim of 36 subjects completing the study.

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 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.

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 between 18 and 40 years.
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 have successfully worn contact lenses within six months of starting the study.
5. They can be satisfactorily fitted with the study contact lenses.
6. They have a contact lens spherical prescription between -0.25 to - 6.00D (inclusive) based on the ocular refraction.
7. They have a spectacle cylindrical correction of -0.75D or less in each eye based on the ocular refraction.
8. They own and habitually wear single vision spectacles.
9. They can attain at least 0.20 logMAR distance high contrast visual acuity in each eye, with the study lenses.
10. They agree not to participate in other clinical research while enrolled on this 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 contraindicate contact lens wear.
2. They have a systemic disorder which would normally contraindicate contact lens wear.
3. They are using any topical medication such as eye drops or ointment.
4. They are aphakic.
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 or pose a risk to study personnel; or they have any immunosuppressive disease (eg HIV) or a history of anaphylaxis or severe allergic reaction.
9. They have grade 3 or greater of any of the following ocular surface signs: corneal oedema, corneal vascularisation, corneal staining, tarsal conjunctival changes or any other abnormality, which would normally contraindicate contact lens wear.
10. They have taken part in any other clinical trial or research, within two weeks prior to starting this study, which may impact on this particular work.

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 an 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 or designee 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 which might impact the study objectives 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
Name	B of n ty	Tota 30
Manufacturer	CooperV s on Inc	A con
Mater a	Comf con A	Lehf con A
EWC (%)	48	55
BOZR (mm)	8.6	8.4
D ameter (mm)	14.0	14.2
Spher ca powers (D)	-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

Each lens type will be worn on a single day for the six hour study period only and then will be discarded.

2.6.2 Care regimen

No care system will be used on this study.

2.6.3 Inventory control

Biofinity lenses will be supplied by CooperVision Inc. Total30 lenses will be sourced by Eurolens Research.

[redacted]. Lenses of interest (such as device deficiencies) which have been stored during the study, will be discarded on completion of the study report, unless advised otherwise by the Industrial Contact Person. Unworn lenses will be destroyed. There will be an accurate accounting of the study test product at the completion of the study. All used study test products will be documented (Lot number; Expiry date etc.).

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 will be masked to the two lenses - the lens foils 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 20 years after completion of the final report. The Sponsor company'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 attended their last visit.

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 four visits – a dispensing visit and a follow-up visit after approximately six hours, for each lens type.

V s t	Target	A owab e range
D spens ng 1	N/A	N/A
Fo ow-up 1	6 hours from d spens ng	5-7 hours
D spens ng 2	N/A	N/A
Fo ow-up 2	6 hours from d spens ng	5-7 hours

Table 3: Visits and allowable ranges.

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 Pre-enrolment

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

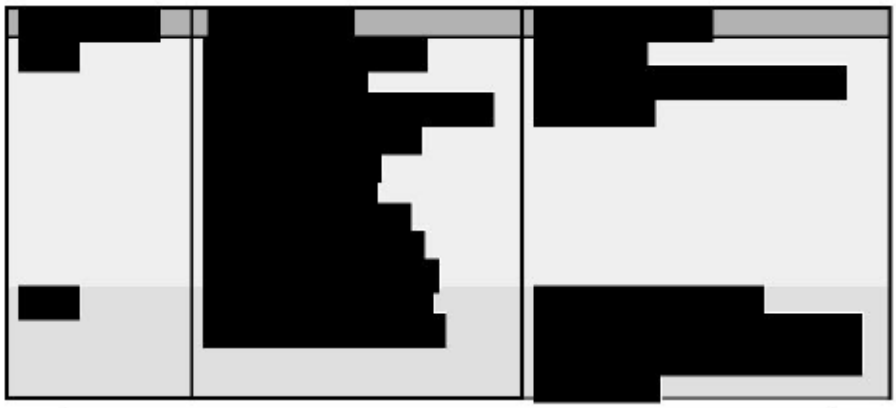
3.2.2 Dispensing 1

Subjects should attend wearing their habitual spectacles.

They 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.

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

1. Details of the ocular, medical and contact lens-wearing histories of the subject will be noted (including habitual lenses, modality, wear time and comfortable wear time).
2. The investigator will perform [redacted] 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'.
3. [redacted]



[redacted]

The presence of any adverse events will be recorded [redacted]

4. 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.
5. The first randomised lens pair will be applied by the subject and allowed to settle for five minutes. To maintain investigator masking, lenses will be pre-prepared and checked, and supplied at the visit to the subject without the investigator inspecting the lenses in their blisters.
6. Monocular logMAR visual acuity (high contrast) will be recorded before performing an over-refraction, and then monocular logMAR visual acuity (high and low contrast) 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'.

7. [redacted]

9. The subject will be asked to score the following subjective scores with reference to appropriate vertical visual analogue scales (0-100) [redacted]):
   - Comfort
   - Vision
   - [redacted]
10. The subject will then be discharged and asked to return for the follow-up visit having worn the study lenses for approximately six hours.

3.2.3 Follow-up 1 (6 hours later)

Subjects should attend wearing the study lenses which should have been in situ for approximately six hours. Subjects who attend without lenses in situ for approximately six hours will usually be rescheduled. 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. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100) [redacted]
   - Overall comfort
   - Vision
   - [redacted]
3. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4. [redacted]
5. [redacted]
6. [redacted]
7. Distance high contrast visual acuity will be assessed in the subject's spectacles.
8. The subject will be discharged from the study visit and will be asked to return for Dispensing 2, wearing their habitual spectacles.

3.2.4 Dispensing 2

Subjects should attend wearing their habitual spectacles.

1. Any changes to medical and ocular histories will be recorded.
2. Steps 3-10 from Dispensing 1 procedures (3.2.2) will be carried out, with the second study lens being fitted at step 5.

3.2.5 Follow-up 2 (6 hours later)

Subjects should attend wearing the study lenses which should have been in situ for approximately six hours. Subjects who attend without lenses in situ for approximately six hours will usually be rescheduled.

1. The same procedures as at Follow-up 1 (3.2.3) will be carried out.
2. At the final visit (or when the subject is discontinued at an earlier visit) the subject will complete the University PR20 form in order for their payment to be processed and then discharged, although they may have been asked by the investigator to attend a post-study follow-up visit. They should continue to use their lenses and solutions as advised, and seek aftercare for their contact lenses.

3.2.6 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 visit(s) 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]

Industrial Contact Person

[redacted]