Clinical investigation plan

C19-679
(EX-MKTG-115)

Vision stability and preference for soft toric vs. soft spherical contact lenses

A clinical evaluation for
CooperVision Inc.

Principal Investigator
Philip Morgan

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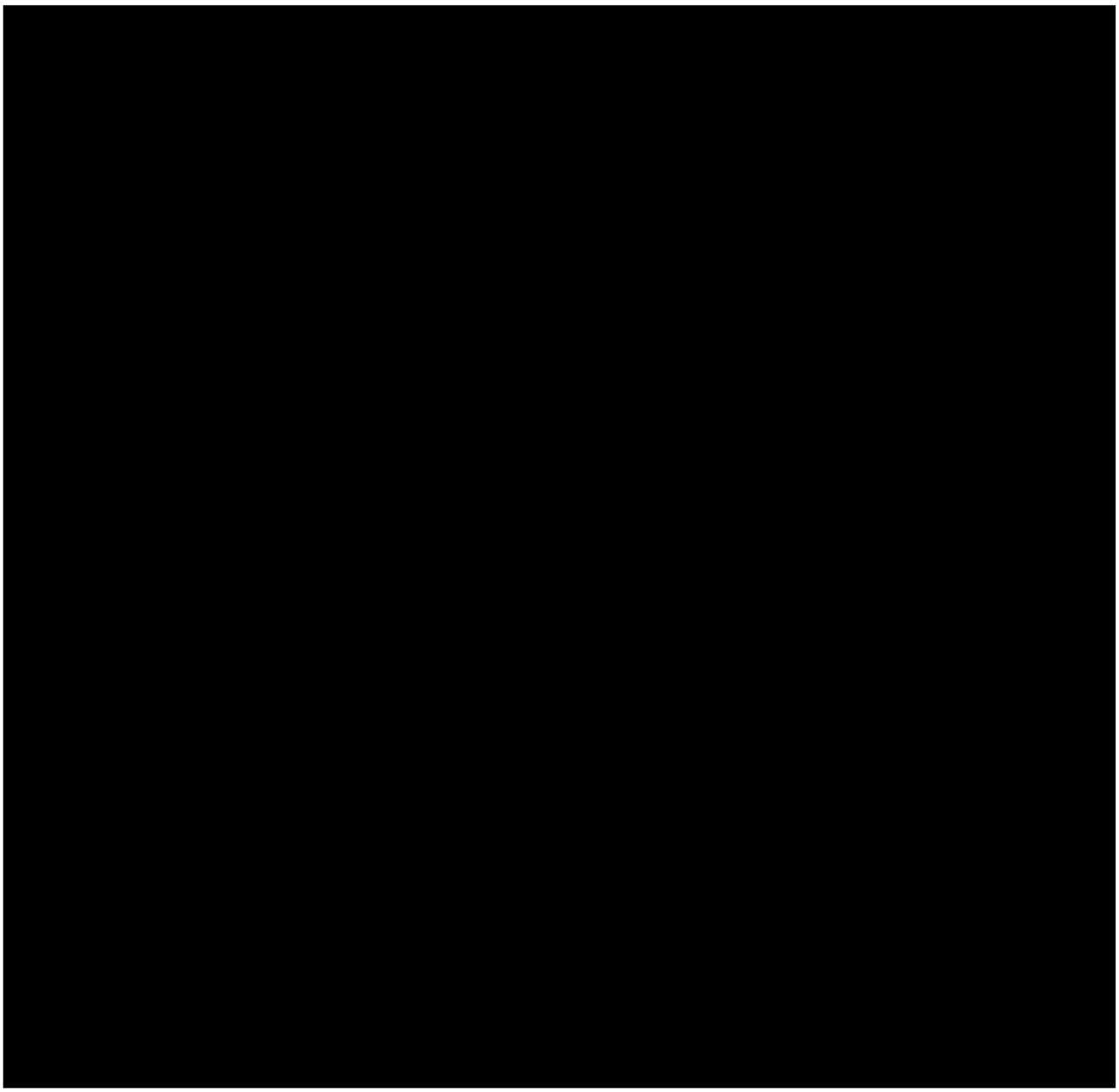
Contents



Study summary

This subject-masked, randomised, bilateral, crossover non-dispensing study will investigate vision stability and preference for soft toric vs. soft spherical contact lenses

Up to thirty subjects will be enrolled onto this study and will wear a pair of toric lenses and a pair of spherical lenses at a single clinic visit, in random sequence. Subjects will be exposed to a range of tasks to explore their vision quality for approximately 30 minutes for each lens pair. [redacted]

A study summary is shown in Table 1.

Visit	Procedures
Study visit	Informed consent taken Explanation of study procedures and subject instructions Ocular, medical and contact lens histories [redacted] Confirmation of eligibility First lens pair fitted Lens fit assessment (acceptable or not for standard fit, and rotation for toric fit) [redacted] First lens pair removed and discarded Second lens pair fitted Lens fit assessment (acceptable or not for standard fit, and rotation for toric fit) [redacted] Payment issued

Table 1: Study summary.

Section 1. Overview

1.1 Background

[redacted]

1.2 Personnel

This work will be conducted at Eurolens Research, The University of Manchester, UK under the general direction of Philip Morgan PhD MCOptom FAAO FBCLA. The Principal Investigator for the work is Philip Morgan PhD MCOptom FAAO FBCLA. Economic analysis will be conducted at the Center for Economic Research and Policy Analysis at Appalachian State University, USA.

1.3 [redacted]

1.4 Study design

This will be a randomised, subject-masked, crossover, bilateral study, controlled by cross-comparison. Thirty subjects will use each lens type at a single visit in random sequence.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that vision stability (the primary outcome measure) with a spherical contact lens correction vs. a toric contact lens correction will be the same. This hypothesis will be tested using linear regression analysis. Lens fit is the secondary outcome variable of interest.

Other hypotheses include [redacted] visual acuity. Other hypotheses in this work will also be tested with linear regression analyses and non-parametric methods. Any 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, similar study, 27 subjects are required to complete the study for 80% power for subjective vision and subjective vision stability, assuming a standard deviation of 1.5 and 1.8 points, on a 0-10 scale and assuming a meaningful difference of 1.0 units. 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 States Food and Drug administration (FDA) and International Organization for Standardization (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'.

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 30 subjects will be consented with the aim of 27 subjects completing the study.

2.1.1 Subject withdrawal and replacement

This study includes one clinical visit. 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 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 18-35 years 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 soft spherical contact lenses in both eyes.
5. They have a spherical component of their spectacle refractive error between -0.50DS and -6.50DS in both eyes.
6. They have a cylindrical component of their spectacle refractive error between -0.75DC and -1.25DC in both eyes.
7. They can be fitted satisfactorily with both lens types.
8. They own an acceptable pair of spectacles.
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 (including comfort drops) or ointment on a regular basis.
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.
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 or repeated refusal to follow instructions. Subjects will be discontinued if a serious adverse event occurs. 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 Appendix A (adverse events are classified as ‘serious’, ‘significant’ or ‘non-significant’). Clinical assessment is made at the study visit 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 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.

Name	Biofinity	Biofinity Toric
Manufacturer	CooperVision Inc	CooperVision Inc.
Material	Comfilcon A	Comfilcon A
EWC (%)	48	48
BOZR (mm)	8.6	8.
Diameter (mm)	14.0	14.5
Spherical powers (DS)	+8.00 to -12.00 (0.25 steps; 0.50 steps after ±6.00)	+8.00 to -10.00 (0.25 steps; 0.50 steps after ±6.00)
Cylinder powers (DC)	n/a	-0.75, -1.25, -1.75, -2.25

Table 2: Study lenses.

2.6.1.1 Use of lenses

Both lens types will be worn 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 will be supplied by CooperVision Inc. All worn lenses will be discarded. Unworn lenses will be returned to:

[redacted]

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 as they will be applied by the optometrist. 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'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 completed the study 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 a single study visit.

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 this 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.

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 Study visit

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 [redacted]:

1. Details of the ocular, medical and contact lens-wearing histories of the subject will be noted [redacted]
2. [redacted]

[redacted]

[redacted]

The presence of any adverse events will be recorded on the CVI AE form [redacted]

3. [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 fitted and allowed to settle for 10 minutes.
6. Lens fit will be assessed (the spherical lens will be classed as either 'acceptable' or 'not acceptable', whereas for the toric lens, in addition to this, rotation will be recorded at 10 minutes). If the toric lens is mislocated more than 5° from the optimal position, a second lens will be applied to correct for this. A maximum of three lenses will be allowed per eye. If the third lens is 10° or less from the optimal position, that lens will be considered to be satisfactory. If the fit is still deemed unsatisfactory the subject will be discontinued and replaced.
7. [redacted]

[redacted]

8. The subject will be asked to perform certain tasks to explore their vision quality: mobile phone use for about two minutes, browsing the web on a desktop computer for about two minutes and walking around the department for five minutes (viewing signage and the 'number plate test'). Subjective vision and vision stability scores will be recorded for each task using a 0-100 visual analogue scales.
9. [redacted]

11. The first lens pair will be removed, and the second fitted and allowed to settle for 10 minutes.
12. Points 6-10 will be repeated for the second lens pair.
13. [redacted]

17. At the final visit (or when the subject is discontinued at an earlier visit) the subject will be issued with their payment and 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.

3.2.3 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 Sponsor Contact Person in order to make comments and ask for re-drafts. If no comments are received from the Sponsor Contact Person within eight weeks, a final report will be released with a separate document control page (in duplicate), requesting the Sponsor 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