Clinical investigation plan

C24-750
(EX-MKTG-159)

A clinical comparison of two multifocal toric soft contact lenses

A clinical evaluation for
CooperVision Inc

Principal Investigator
Carole Maldonado-Codina

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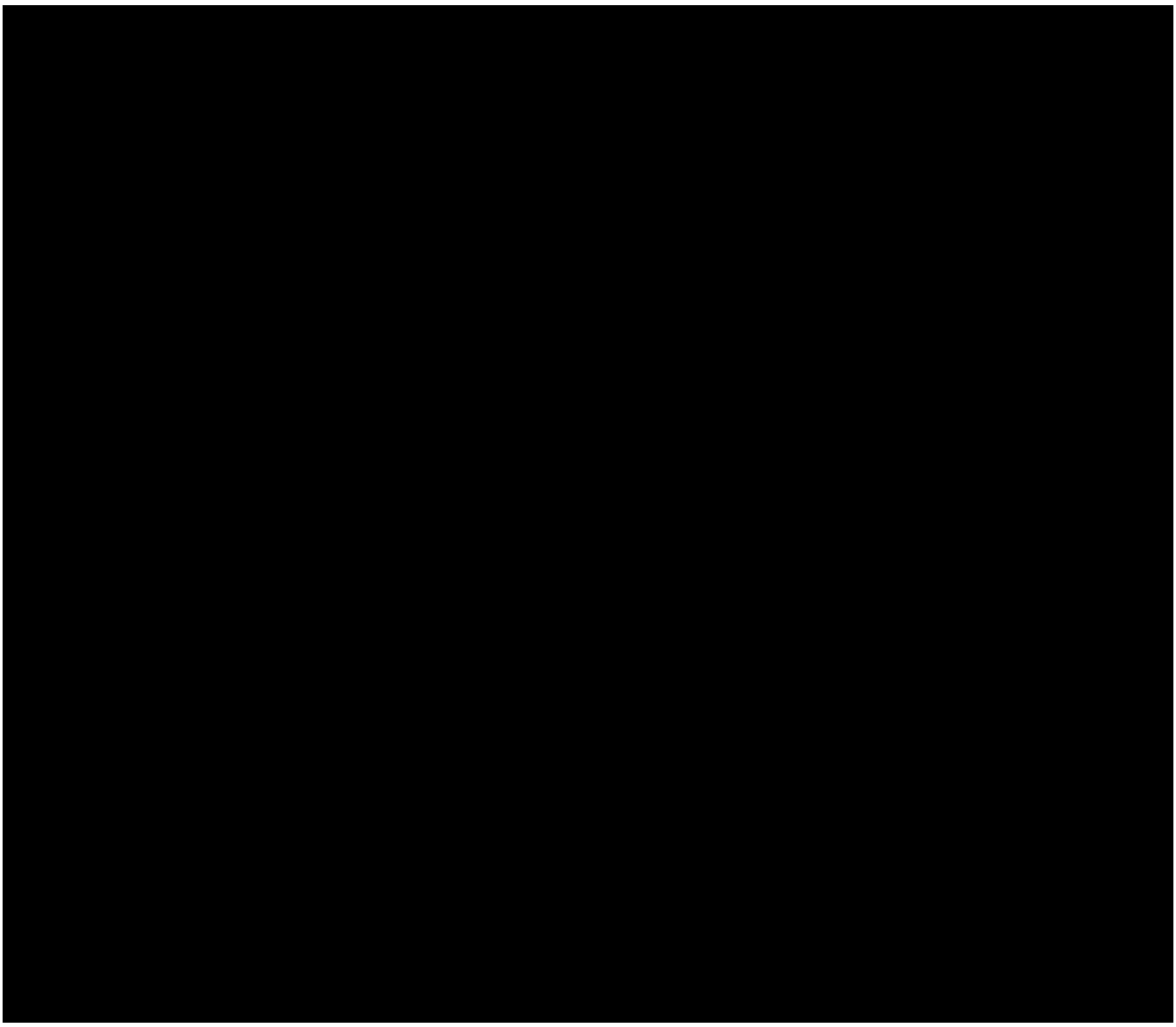

Study summary

This subject-masked bilateral non-dispensing crossover study will compare the clinical performance and subjective acceptance of the Proclear Multifocal Toric and Biofinity Toric Multifocal soft contact lenses.

Up to 40 subjects will be consented with the aim of completing at least 30 subjects. Each subject will attend an initial visit at which the ideal lens specifications for each lens brand will be determined and ordered. At the second visit, all subjects will be fitted with the Proclear Multifocal Toric lens first followed by the Biofinity Toric Multifocal lens. [redacted]

A study summary is shown in Table 1.

Visit	Procedures
Visit 1	Informed consent Explanation of study procedures and subject instructions Ocular, medical and contact lens histories [redacted] Inclusion/exclusion criteria confirmed Proclear MFT fitted (from fitting bank) 15 minutes after application: [redacted] Determination of ideal contact lens specification Proclear MFT removed and Biofinity TMF applied (from fitting bank) 15 minutes after application: [redacted] Determination of ideal contact lens specification Study lenses ordered
Visit 2	Changes to general and ocular health and medications [redacted] Proclear MFT applied 1 minute after application: [redacted] Lenses removed Biofinity TMF applied [redacted]

	Lenses removed [redacted] Payment processed

Table 1: Study summary.

Section 1. Overview

1.1 Background

This project seeks to compare the clinical performance of the Proclear Multifocal Toric and Biofinity Toric Multifocal 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 two study contact lenses.

1.4 Study design

This will be a subject-masked, bilateral study, controlled by cross-comparison. Up to 40 subjects will wear the Proclear Multifocal Toric and the Biofinity Toric Multifocal lens in the clinic only, following an initial visit to determine ideal lens specifications.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that subjective scores for the lenses will be substantially equivalent. The primary outcome variable is subjective distance vision.

[redacted] As such, these will be compared using linear regression models or other parametric methods. [redacted] Deviations from this 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 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.

1.5.2 Power analysis

Using data from a previous study with multifocal contact lenses, minimum intra-subject standard deviation values on a 0-100 scale for comfort, distance vision, near vision and overall score were 18, 16, 19 and 17 units, respectively. Assuming a meaningful difference of 10 units and an alpha of 0.05, data from 30 subjects are required to provide power of 0.80 or greater for equivalence testing for these four parameters. To allow for ineligible subjects and discontinuations, up to 40 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 Organisation (ISO) guidelines due to the daily wear nature of the study. The work where practical will be conducted in accordance with:

- ICH Good Clinical Practice Guidelines
- BS EN ISO 14155 'Clinical investigation of medical devices for human subjects - Good clinical practice'
- Declaration of Helsinki

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).

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

2.1.1 Subject withdrawal and replacement

This study includes two 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 initial 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 35 years or over and have capacity to volunteer.
2. They understand their rights as a subject and are willing 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 are currently wearing soft contact lenses or have done so within the past 12 months.
6. They have a spherical prescription between +10.00 and -10.00DS inclusive, (based on the ocular refraction).
7. They have astigmatism of between -0.75 and -5.75DC (based on the ocular refraction) in each eye.
8. They have a reading addition component to their spectacle refraction of between +0.75 and +2.50DS.
9. They can be satisfactorily fitted with the study lenses.
10. They own a wearable pair of spectacles.

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 contra-indicate contact lens wear.
3. They are using any topical medications 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 have any ocular abnormality which would, in the opinion of the investigator, normally contraindicate contact lens wear.
8. They have eye or health conditions including immunosuppressive or infectious diseases which would, in the opinion of the investigator, contraindicate contact lens wear or pose a risk to study personnel; or a history of anaphylaxis or severe allergic reaction.
9. 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 who choose to leave the study at their own request will be replaced. 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 responsibilities

The investigator will be appropriately qualified, have suitable resources to conduct the study, have study training, ensure subject safety and data integrity. At all times they 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 their participation in the clinical study.

2.3.2 Investigator reporting responsibilities

In the case of a 'serious' or 'significant' adverse event, the Principal Investigator will notify the Sponsor 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 Sponsor 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

These are unanticipated or unintentional changes that occur after Manchester UREC approval. Any deviations, major (affect the integrity of the study and/or subject safety) or minor from this protocol will be recorded, and reported to the Sponsor as appropriate. Manchester UREC will be informed as necessary.

2.5.1 Protocol amendments

Amendments will be agreed between the Sponsor 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.

	First lens	Second lens
Lens name	Proclear Multifocal Toric	Biofinity Toric Multifocal
Manufacturer	CooperVision	CooperVision
Material	Omafilcon A	Comfilcon A
EWC (%)	59	48
BOZR (mm)	8.8	8.7
Diameter (mm)	14.4	14.5
Spherical powers (D)	+10.00 to -10.00 (0.50D steps after -6.50)	-10.00 to -6.50(0.50 steps) -6.00 to +6.00 (0.25 steps)

		+6.50 to +10.00 (0.50 steps)
Cylinder powers (D)	-0.75 to -5.75	-0.75 to -5.75
Axes (degrees)	5 to 180 (5 degree steps)	5 to 180 (5 degree steps)
Add (D) Multifocal design	+1.00 to +4.00 Centre distance (D) and centre near (N)	+1.00 to +2.50 Centre distance (D) and centre near (N)

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

Both Proclear Multifocal Toric and Biofinity Toric Multifocal lenses will be supplied by CooperVision Inc.

Lenses of interest such as those with device deficiencies will be stored and reported to the Sponsor. If the lens is likely to have caused or contributed to a serious adverse event, this will be reported as soon as possible.

Lenses which have been stored during the study, will be discarded on completion of the study report, unless advised otherwise by the Sponsor. All study lenses will be destroyed at the end of the study.

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.) in the study CRF.

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. Subjects will be masked to the two lens types by means of the investigator opening the lens packaging and ensuring that the subject does not see the lens foil details. Masking may be 'broken' if deemed necessary, by the Principal Investigator or Sponsor.

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 attended their last visit.

2.11 Subject confidentiality

All matters related to this work will remain confidential within Eurolens Research, the Sponsor 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 subjects 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. Review study product accountability.
6. Document their observations and make them available to relevant authorised parties (e.g. Manchester UREC).
7. 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. Visit 1 will determine the ideal contact lens specifications, and visit 2 will assess both lens types. Subjects may wear their habitual contact lenses and/or spectacles between the two visits.

Visit	Target	Allowable range
Visit 1	N/A	N/A
Visit 2	N/A	N/A

Table 3: Visits and allowable ranges.

3.1.1 Repeat visit 1

Should a subject attend visit 1 and be ineligible for the study owing to a reason which the investigator believes to be transient [redacted] 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 Unscheduled visits

An unscheduled visit is an interim visit requested by the subject or investigator due to an unanticipated event. [redacted]

3.1.3 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 giving written consent.

3.2.2 Informed consent

The subject will be required to sign an informed consent form prior to enrolment (Appendix B) and before any procedures specific to the clinical investigation are performed. 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.

3.2.3 Visit 1

Subjects should attend wearing their spectacles.

Written consent from the subject will be obtained as detailed in section 3.2.2.

Subjects will be instructed on the following:

1. [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 (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 [redacted]
2. [redacted].
3. [redacted]
4. [redacted]
5. [redacted]

The presence of any adverse events will be recorded

6. 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 the investigator deems the ineligibility to be transient (section 3.1.1), this initial visit may be repeated.
7. Using the fitting set, the Proclear Multifocal Toric lens will be applied and allowed to settle for 15 minutes. The closest available lens specification to the subject's prescription will be selected.
8.
9. The Proclear Multifocal Toric lenses will be removed.
10. Using the fitting set, the Biofinity Toric Multifocal lenses will be applied and allowed to settle for 15 minutes. The closest available lens specification to the subject's prescription will be selected.
11.
12. The Biofinity Toric Multifocal lenses will be removed.
13.
14.
15. The study lenses will be ordered, taking into account the manufacturers fitting guide
16. The subject will then be notified of expected timelines for lens receipt and will be subsequently contacted to arrange visit 2. Subjects may wear their habitual lenses and/or spectacles between the two visits.

3.2.4 Visit 2

1. Any changes to ocular or general health and medication will be recorded.

2. [redacted]

4. The Proclear MFT lenses will be applied and allowed to settle for one minute.
5. [redacted]
6. The subject will be allowed to adapt to the lenses away from the consulting room for 15 minutes.
7. After 15 minutes adaptation, the subject will return to the clinic.
8. [redacted]
9. [redacted]
10. [redacted]
11. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100)[redacted]:
    - [redacted]
    - Distance vision
    - [redacted]
    - [redacted]
8. The Proclear MFT lenses will be removed.
9. The Biofinity TMF lenses will be applied and allowed to settle for one minute.
10. [redacted]
11. The subject will be allowed to adapt to the lenses away from the consulting room for 15 minutes.
12. [redacted]

15. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100)[redacted]:
    - [redacted]
    - Distance vision
    - [redacted]
    - [redacted]

16. The Biofinity TMF lenses will be removed.
17. [redacted]
18. [redacted]
20. At the final visit (or when the subject is discontinued at an earlier visit) the subject will either be provided with a cash payment [redacted] They will then be 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 if applicable) as advised, and seek aftercare for their contact lenses.

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 visit(s) by verbal questioning of the subject by the investigator.

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 in order to make comments and ask for re-drafts. If no comments are received from the Sponsor within eight weeks, a final report will be released with a separate document control page, requesting the Sponsor to sign and return 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 Sponsor company.

4.3 Personnel