Clinical investigation plan

[redacted] (CV-16-28)

A clinical comparison of the Biofinity XR Toric Multifocal and Proclear Toric XR Multifocal contact lenses

A clinical evaluation for
CooperVision Inc.

Study Leader

[redacted]

Principal Investigator

[redacted]

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Contents

Document control

Study title:	A clinical comparison of the Biofinity XR Toric Multifocal and Proclear Toric XR Multifocal contact lenses (C16-599)
Sponsor company:	CooperVision Inc.
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It is acknowledged and agreed that the work to be performed under this protocol is governed by the terms and conditions of the Annual Agreement (C16-ANN) entered into by the [redacted] and CooperVision Inc. dated October 28, 2015.

Document author:

Document approved by:

Document reviewed by:

Document reviewed and approved by:

[redacted]

Section 1. Overview

1.1 Background

This project seeks to compare the clinical performance and subjective acceptance of the Biofinity XR Toric Multifocal and the Proclear Toric XR Multifocal soft contact lenses (both CooperVision Inc.). CooperVision (CVI) is extending the power range of the commercially available Biofinity Toric silicone hydrogel contact lenses to include multifocals. The extended power range for Biofinity Toric for subjects requiring a multifocal product will be called Biofinity XR Toric Multifocal. The Proclear Toric XR Multifocal is an existing lens which will be used as the control lens.

1.2 Personnel

[redacted]

1.3 Study objectives

This study aims to compare the clinical performance and subjective acceptance of the Biofinity XR Toric Multifocal and the Proclear Toric XR Multifocal soft contact lenses.

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 for two weeks in random sequence. Follow-up visits for each lens will be performed after two weeks of wear. Lenses will be worn on a daily wear basis.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that subjective scores and visual acuity for the lenses will be substantially equivalent.

[redacted]

1.5.1 Power analysis

In order to determine the study sample size, power analysis was employed using subjective vision data from a previous clinical study. In order to achieve 80% power to detect a difference of 10 units for subjective vision (assuming an alpha of 0.05 and two-tailed paired analysis), 16 completing subjects are required. In order to achieve 80% power to detect a difference of half a line on a LogMAR chart (assuming an alpha of 0.05 and two-tailed paired analysis), 22 completing subjects are required. To allow for discontinuations, 30 subjects will be recruited.

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. [redacted]). 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 up to 30 subjects will be recruited and enrolled.

2.1.1 Subject withdrawal and replacement

This study includes three 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 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:

[redacted]

2.1.3 Inclusion criteria

Subjects will only be eligible for the study if:

1. They are aged 40 - 70 years, inclusive.
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 completed the non-dispensing study (C16-597) as the lenses to be worn on this study (C16-599) are predetermined from their participation on study C16-597.
5. They have a contact lens spherical prescription between +10.00 to -10.00D (inclusive).
6. They have astigmatism between of -0.75 and -5.75DC (based on the calculated ocular refraction) in each eye.
7. They have an Add component to their spectacle refraction (between +0.75 and +2.50DS).
8. They can be satisfactorily fitted with the study lenses.

9. They can attain at least 0.30 logMAR binocular distance high contrast visual acuity with the study lenses within the available power range.
10. They have successfully worn soft contact lenses in the last two years.
11. They are willing to comply with the wear schedule (at least five days per week and for at least six hours per day).
12. They agree not to participate in other clinical research for the duration of this study.
13. 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 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 breast-feeding.
8. They have any clinically meaningful slit lamp findings contraindicating contact lens wear (e.g. ≥ Grade 3 finding of oedema, corneal neovascularisation, corneal staining, tarsal abnormalities, conjunctival injection, blepharitis/meibomian gland dysfunction) on the Efron classification scale or any other ocular abnormality that in the opinion of the investigator would contraindicate contact lens wear.
9. They have any infectious disease (e.g. hepatitis) 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).
10. They have a history of anaphylaxis or severe allergic reaction.
11. 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 adverse events listed in Appendix A (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 adverse event will be reported on the case report forms and described 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. [redacted] 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. [redacted]

2.5 Protocol deviations

Any deviations from this protocol will be recorded and reported to the Industrial Contact Person as appropriate. [redacted]

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. [redacted]

2.6 Study resources

Study products will be stored according to the manufacturer's product instructions.

2.6.1 Lenses

Details of the study lenses are provided in Table 2. The Proclear Toric XR Multifocal lens is currently CE marked and the Biofinity XR Toric Multifocal lens is currently undergoing CE marking. The study will not commence until this lens has CE approval. Initial lens selection will be as indicated by the manufacturers' fitting guidelines.

	Test lens	Control lens
Name	Biofinity XR Toric Multifocal	Proclear Toric XR Multifocal
Manufacturer	CooperVision	CooperVision
Material	Comfilcon A	Omafilcon B
EWC (%)	48%	62%
Base Curve (mm)	8.7	8.4 / 8.8
Diameter (mm)	14.5	14.4
Spherical powers (DS)	+10.00 to -10.00 (0.50 steps after ±6.50D)	+20.00 to -20.00 (0.50 steps after -6.50D)
Cyl Powers (DC)	-0.75 to -5.75 (0.50 steps)	-0.75 to -5.75 (0.50 steps)
Axis	5 to 180 (5 degree steps)	5 to 180 (5 degree steps)
Add	+1.00 to +4.00 (D & N)	+1.00 to +4.00 (D & N)

Table 2: Study lenses.

2.6.1.1 Use of lenses

All lens types will be worn on a daily wear basis. Lenses should be worn for a minimum of six hours per day, five days per week. The lenses should also be worn for a minimum of two hours before attending the follow-up visits.

2.6.2 Care regimen

Subjects will use Synergi (CooperVision Inc.) Multi-Purpose Solution including a 'rub and rinse' step. Subjects can also use comfort/lubricating drops (Blink Contacts manufactured by AMO) if this is necessary.

2.6.3 Inventory control

CooperVision Inc. will supply both lens types and the lens care system. [redacted] will supply any comfort/lubricating drops.

All worn lenses will be discarded. Unworn lenses will be retained [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.

2.8 Documentation

Documents related to this work that require archiving will be kept [redacted] 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 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 complete when all subjects have signed the exit statement.

2.11 Confidentiality

All matters related to this work will remain confidential within [redacted], the funding company and any regulatory authority [redacted]). [redacted] 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. [redacted]

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 [redacted]
6. Implement [redacted] clinical monitoring standard operating procedure.

Section 3. Subject management

3.1 Visit scheduling

Subjects will be required to attend three visits – an initial/dispensing visit, and two follow-up visits. Follow-up visits will take place after two weeks of contact lens wear for each lens type. Acceptable date ranges are shown in Table 3.

Visit	Target	Allowable range
Initial/Dispensing 1	N/A	N/A
Follow-up 1/Dispensing 2	14 days from Dispensing 1	10-18 days from Dispensing 1
Follow-up 2/ Exit	14 days from Dispensing 2	10-18 days from Dispensing 2

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.

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 [redacted] 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 time to suit themselves, each subject will be asked to watch a short on-line information presentation detailing study visits and procedures. They will be asked to complete multiple-choice questions to gauge their understanding of the study. Upon successful completion of these questions, an email is sent automatically to [redacted], and the subject is contacted to arrange their initial visit.

3.2.2 Initial/Dispensing 1 visit

Subjects should attend this visit wearing their spectacles. They will be required to sign an informed consent form prior to enrolment (Appendix C). 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:

- Lens handling, application and removal, where necessary.
- Specific study instructions, such as the importance of not using any other contact lens products.
- 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 today. Average wear time and comfortable wear time over the last two weeks).
2. Subject iris colour will be recorded.
3. Auto-keratometry measures will be recorded.
4. The investigator will perform refraction and high illumination distance and near (40cm) logMAR visual acuity (binocular and monocular, high and low contrast for both distances), in accordance with the current [redacted] Standard Operating Procedure 'The set up, measurement of visual acuity and procedures for carrying out an over refraction using the [redacted] computerised logMAR VA chart'.
5. The optimal (habitual) reading distance will be recorded and binocular high contrast visual acuity at high illumination will be recorded using a near logMAR chart. The range of clear near vision will also be recorded.
6. Low illumination (100-120 lux) near visual acuity at 40 cm will be recorded as well as the range of clear vision.
7. [redacted]

11. [redacted]

Classification	Primary signs	Secondary signs
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]

[redacted]

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

12. 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.
13. The first lens pair will be fitted according to the randomisation table [redacted] and in accordance to the manufacturer's fitting guide. The subject will be masked from the lens type, but will apply the lenses themselves without taking note of the position of any visible markings.
14. Lens rotation and stability will be observed after one, three and 10 minutes of lens settling. Nasal lens rotation is recorded as a positive number and temporal rotation is recorded as a negative number. Following the final 10 minute recording, overall stability will be graded using the grading scales [redacted]
15. The visibility of the toric markings will be graded after the three minute toric lens fit recording using the grading scales [redacted]. The investigator will be encouraged to make comments on the visibility in addition to grading.

[redacted]

17. Following the last 10 minute toric fit recording, lens fit will then be assessed using the following evaluations: horizontal and vertical centration, corneal coverage and movement. Normally, for an acceptable fit, centration and movement will fall within currently accepted clinical criteria [between -1 and +1 on a -2 to +2 grading scale [redacted]

18. [redacted]
19. An overall grade for lens fit acceptance will be provided for both general lens fit and toric lens fit measures using the grading scales [redacted].
20. High illumination, high contrast distance monocular and binocular visual acuity will be recorded using distance logMAR charts before and after spherical over-refraction.
21. High illumination, high contrast near monocular and binocular visual acuity will be recorded at 40 cm using near logMAR charts.
22. High illumination, high contrast near binocular visual acuity will be recorded at the optimal reading distance using near logMAR charts (without over-refraction). The range of clear near vision will also be recorded.
23. [redacted]
26. The lens care system will be explained and dispensed.
27. The subject will be asked to return two weeks later having worn lenses for a minimum of six hours and five days a week.

3.2.3 Two-week follow-up/dispensing 2 visit

Subjects should attend wearing the study lenses which should have been in situ for at least two hours. Subjects who attend without lenses in situ for at least two hours will usually be rescheduled. The following procedures will be performed:

1. Lens wearing time on study visit day will be recorded.
2. Any study products relating to the previous two weeks of the study will be collected.
3. Details of the contact lens wear since the previous visit will be recorded (including wear time and comfortable wear time).
4. The subject will be asked to score the following with reference to appropriate visual analogue scales (0-100) as outlined in the 'Subjective ratings' document in [redacted]

[redacted]

- ∞ Overall comfort
- ∞ Dryness during the day

[redacted]

- ∞ Visual fluctuation/stability

[redacted]

- ∞ Overall handling
- ∞ Overall satisfaction
- ∞ Distance vision
- ∞ Intermediate vision
- ∞ Near vision
- ∞ Near vision in dim illumination
- ∞ Ghosting at distance
- ∞ Ghosting at near
- ∞ [redacted]
- ∞ Vision whilst driving during the day
- ∞ Vision whilst driving at night
- ∞ [redacted]

[redacted]

6. High illumination, high and low contrast distance and near (40 cm) monocular and binocular visual acuity will be recorded using distance and near logMAR charts before over-refraction. The range of clear vision at near (binocularly) will also be recorded for high contrast measures.
7. High illumination, binocular high contrast near visual acuity will be recorded at the subject's habitual working distance (which was recorded at the initial visit) using a near logMAR chart.
8. Spherical over-refraction will be performed on each eye if binocular distance high contrast visual acuity is less than 0.2. High illumination, high and low contrast distance and near (40 cm) monocular and binocular visual acuity will be recorded using distance and near logMAR charts. The range of clear vision at near (binocularly) will also be recorded for high contrast measures.

[redacted]

11. Lens rotation and stability will be recorded.
12. Lens fit and surface will be recorded as described in Section 3.2.1.

[redacted]

15. An overall grade for lens fit acceptance will be provided for both general lens fit and toric lens fit measures using the grading scales [redacted].

[redacted]

18. The lenses will then be removed and discarded.
19. Slit lamp biomicroscopy will be carried out, as detailed in section 3.2.1. The presence of any adverse events will be recorded [redacted]
20. The second lens pair will be applied (according to the randomisation table). The subject will be masked from the lens type, but will apply the lenses themselves without taking note of the position of any visible markings.
21. The steps outlined in Section 3.2.1, 13-25 will be repeated.
22. A new bottle of solution and a new case will be issued.
23. The subject will be discharged and asked to return for the four-week follow-up visit. Subjects should be asked to wear their lenses for a minimum of six hours per day, five days per week and to have worn lenses for at least two hours prior to attending the next scheduled visit.

3.2.4 Four week follow-up/exit visit

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

The same procedures as at the two week follow-up (Section 3.2.3) will be carried out except that no more lenses will be dispensed. The following additional procedures will be carried out:

[redacted]

6. On 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.
7. The subject will be issued with their payment and all study products will be collected.

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 [redacted], 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 sign both copies, one to keep and the other to be returned to [redacted].

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

Study Leader

[redacted]

Principal Investigator

[redacted]

Director

[redacted]

Operations Manager

[redacted]

Investigators

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Project Officer

[redacted]

Study Monitor

[redacted]

Research Administrators

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Industrial Contact Person

[redacted]

[redacted]

[redacted]