Clinical investigation plan

C19-683

(EX-MKTG-116)

Quantification of the visual benefits of soft toric contact lenses compared to soft spherical contact lenses over a range of refractive astigmatism

A clinical evaluation for
CooperVision Inc.

Principal Investigator
Michael Read

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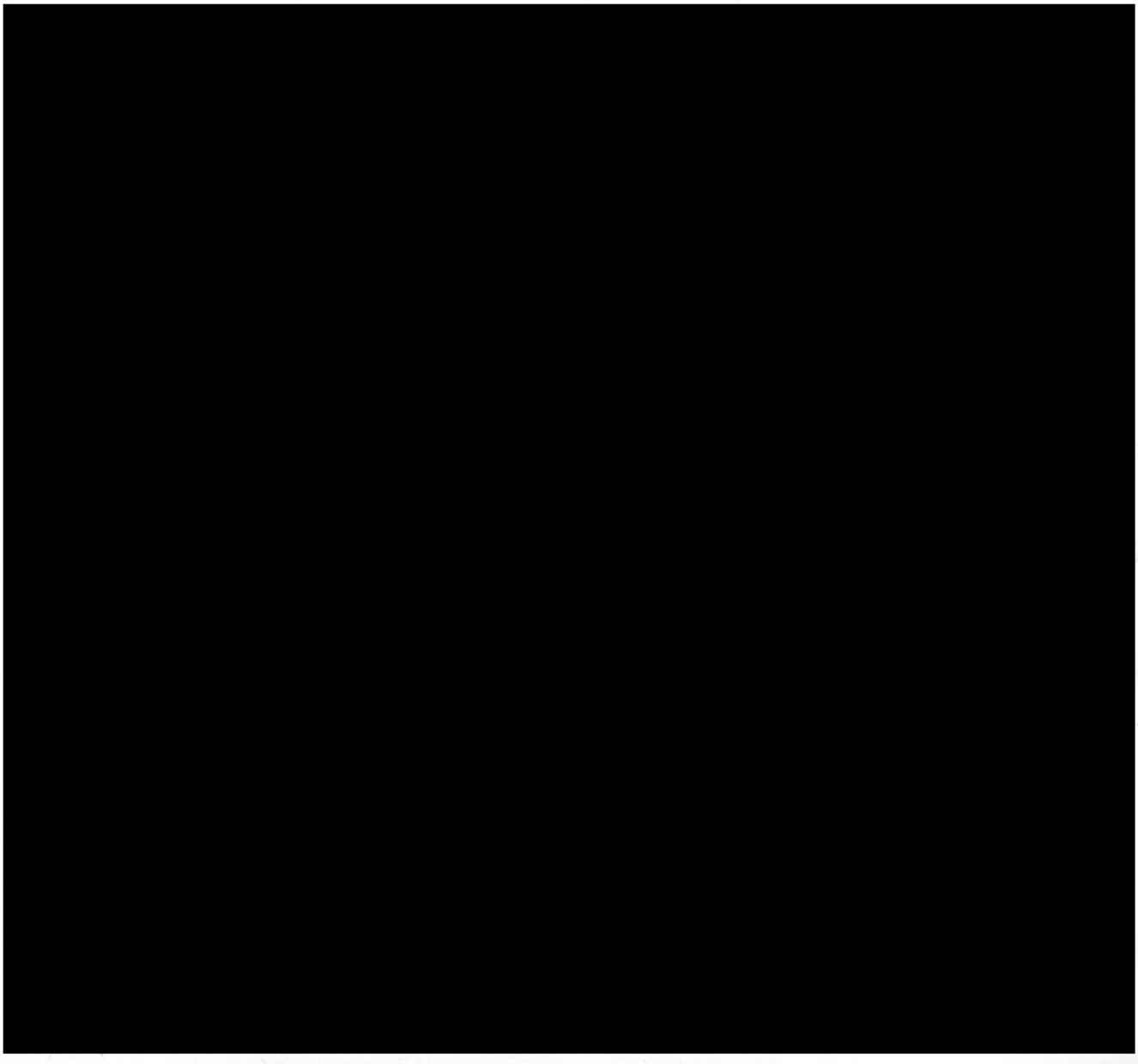
Contents



Study summary

This randomised, crossover, partially masked (for contact lenses), non-dispensing study will compare the clinical performance and subjective acceptance of a custom-made soft toric Biofinity XR contact lens, a soft spherical Biofinity contact lens and a spectacle lens correction, across a range of levels of astigmatism and for three different pupil sizes.

Up to 55 subjects will be enrolled onto this study. At the initial visit, each subject will be fitted with Biofinity spherical and toric contact lenses, in either one or both eyes, depending on whether their astigmatic error falls within the required range. Custom-made Biofinity XR Toric lenses and Biofinity spherical lenses will then be ordered. At visit 2, each subject will wear a spherical Biofinity lens type, a custom-made Biofinity XR Toric lens type and a spectacle correction, in a random sequence for approximately 30 minutes. The optical corrections will be worn in one eye only, with the other eye patched. The following will be assessed throughout the visit: ocular physiology, [redacted], high contrast and low contrast visual acuities for three different pupil sizes [redacted] If both of the subject's eyes are suitable for the study, they will return for visit 3, where the procedures at visit 2 will be repeated for the other eye. A study summary is shown in Table 1.

V s t	Procedures
In t a v s t (may be repeated)	Informed consent taken Exp anat on of study procedures and sub ect nstruct ons Ocu ar, med ca and contact ens h stor es Auto-keratometry [redacted] v sua acu ty B om croscopy F tt ng of tor c tr a ens/ enses V sua acu ty [redacted] F tt ng of spher ca tr a ens/ enses V sua acu ty and over refract on Custom-made tor c and spher ca contact enses ordered
V s t 2 (f rst eye eva uat on) (may be repeated)	Med ca or ocu ar ssues s nce the r ast v s t Entrance b om croscopy and VA Patch ng of the eye not be ng stud ed F tt ng of f rst random sed ens correct on HC and LC v sua acu ty w th d fferent pup s zes [redacted] F tt ng of second random sed ens correct on HC and LC v sua acu ty w th d fferent pup s zes [redacted] F tt ng of th rd random sed ens correct on HC and LC v sua acu ty w th d fferent pup s zes [redacted] Ex t b om croscopy and VA Payment ssued (f v s t 3 not app cab e)
V s t 3 (f app cab e) (fe ow eye eva uat on) (may be repeated)	Med ca or ocu ar ssues s nce the r ast v s t Entrance b om croscopy and VA Patch ng of the eye not be ng stud ed F tt ng of f rst random sed ens correct on (n the other eye to that used at V s t 2) HC and LC v sua acu ty w th d fferent pup s zes [redacted] F tt ng of second random sed ens correct on HC and LC v sua acu ty w th d fferent pup s zes

	[redacted] F tt ng of th rd random sed ens correct on HC and LC v sua acu ty w th d fferent pup s zes [redacted] Ex t b om croscopy and VA Payment ssued

Table 1: Study summary.

Section 1. Overview

1.1 Background

In some contact lens markets, the use of soft toric lenses is significantly lower than might be expected for the range of astigmatism in the population. The reasons for this are varied, but appear to include practitioner reluctance to fit and prescribe such lenses due to a perception of a limited clinical benefit in doing so. This study seeks to provide clinical data to highlight the benefits of prescribing soft toric lenses to astigmats.

1.2 Personnel

[redacted]

1.3 Study objectives

The aim of this work is to undertake a range of vision-related measures with soft toric contact lenses (custom-made Biofinity XR Toric), soft spherical contact lenses (Biofinity) and spectacle lens correction across a range of levels of astigmatism, seven intervals from 0.00DC to -1.50DC, and for three different pupil sizes. Pupil size will be controlled using a novel, automated room lighting/feedback system. This will lead to a quantification of the visual benefit of torics vs. spheres, and allow for the identification of the astigmatic threshold where the difference between these two lens designs becomes clinically meaningful.

1.4 Study design

This will be a randomised, crossover, partially subject-masked (for contact lenses only), non-dispensing study, controlled by cross-comparison. Many subjects will have both eyes within the astigmatism range, and data from two eyes for these subjects will be in the analysis. Some subjects may only have one eye in range. Subjects with two suitable eyes will attend for three visits and those with only one suitable eye will attend for two visits. At the initial study visit, up to 55 subjects will be fiited with the toric (Biofinity XR toric) and spherical (Biofinity) contact lenses in order to provide 12 eyes in each of the seven cylinder powers studied (0.00 to -1.50DC). At visit 2, each subject will wear the spherical contact lens, custom-made toric contact lens and spectacle correction, in a randomised sequence. Visual acuity will be assessed for three different pupil sizes [redacted] using the novel automated room lighting/feedback system. [redacted] During clinical evaluation the eye which is not being studied will be patched. For subjects with both eyes within the required astigmatism range, they will return for visit 3, where the procedures undertaken at visit 2 will be repeated on the fellow eye.

1.5 Statistical considerations

The principal hypothesis to be tested in this work is that visual acuity [redacted] for the different lens corrections and pupil sizes will be the same.

Visual acuity assessment, biomicroscopy gradings [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 may be necessary due to differences between the actual data distribution compared with the anticipated data distribution.

1.5.1 Power analysis

An *a priori* power analysis has determined that 12 eyes are required for each 0.25DC level of astigmatism to provide 80% power to detect a meaningful difference of 0.1 logMAR units between correction types. To evaluate the seven intervals from 0.00DC to -1.50DC, 84 eyes are required.

This analysis assumes a two-tailed paired analysis and an alpha of 0.05. To allow for discontinuations, up to 55 subjects will be fiited with the study lenses.

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 and non-invasive study procedures. Subjects may not benefit directly from taking part in this study; however, information from this study may help researchers gain new insights about contact lens wear and to help others in the future. 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 55 subjects will be fitted with the study lenses, with the aim of 84 eye evaluations completing the study (12 per cylinder power in 0.25DC steps, from 0.00 to -1.50DC).

2.1.1 Subject withdrawal and replacement

This study includes three clinical visits (two clinical visits if only one eye is suitable). 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 of legal age 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 are current wearers of any soft contact lens (i.e. have worn lenses in the last six months).
5. They have refractive ocular astigmatism between 0.00DC and -1.50DC in one or both eyes.
6. They have a spherical component to their ocular refractive error between 0.00 and -6.00 DS.
7. They could attain at least 0.10 logMAR distance high contrast visual acuity in one eye with the study lenses within the available power range.
8. They can be fitted satisfactorily with both lens types.
9. They own an acceptable pair of spectacles.
10. They agree not to participate in other clinical research for the duration of 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 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 corneal refractive surgery.
5. They have any corneal distortion resulting from previous hard or rigid lens wear or have keratoconus.
6. They are pregnant or breastfeeding.
7. They have any ocular abnormality which would, in the opinion of the investigator, normally contraindicate contact lens wear.
8. They have an amblyopic eye, in which case only dominant eye will be assessed for that subject.
9. They have an infectious disease (e.g. hepatitis), any immunosuppressive disease (e.g. HIV) or diabetes.
10. They have a history of severe allergic reaction or anaphylaxis.
11. They have taken part in any other contact lens 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 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 [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 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	B of n ty XR Tor c	B of n ty Sphere	B of n ty Tor c*
Manufacturer	CooperV s on Inc	CooperV s on Inc	CooperV s on Inc
Mater a	Comf con A	Comf con A	Comf con A
EWC (%)	48%	48%	48%
BOZR (mm)	8.7	8.6	8.7
D ameter (mm)	14.5	14.0	14.5
Spher ca powers (DS)	p ano to -6.00D	p ano to -6.00D	p ano to -6.00D
Cy nder powers (DC)	Custom-made 0.00 to -1.50 (0.25 steps)	n/a	-0.75 and -1.25

Table 2: Study lenses. *The Biofinity Toric lens is used for trial fitting only.

2.6.1.1 Use of lenses

This is a non-dispensing study. Subjects will wear the contact lenses in the clinic only. (i.e. lenses will be removed at the end of the study visit and discarded).

2.6.2 Care regimen

No care system will be used on this study.

2.6.3 Inventory control

A bank of Biofinity Toric lenses (used for fitting at visit 1 only), custom-made Biofinity XR lenses (used for clinical evalution at visits 2 and 3) and spherical Biofinity lenses (used for all visits) will be supplied by CooperVision Inc. Wide aperture trial frame lenses will be used to provide optimal spectacle correction at study visits 2 and 3. All worn contact lenses will be discarded. On completion of this study, unworn contact lenses will be discarded and a copy of the lens destruction form will be sent to the sponsor. There will be an accurate accounting of the study test product at the completion of the study. All used study test products will be recorded (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 contact lens types (toric versus spherical) – contact lenses will be over-labelled.

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 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. Ensure accountability of the study test product.
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 or three visits depending on the suitability of one or both of the subject's eyes – an initial visit and one or two follow-up visits accordingly. Subjects may need to attend a repeat study visit. Acceptable date ranges are shown in Table 3.

V s t	Target	A owab e range
In t a / ens f t	N/A	N/A
V s t 2 / 1st eye eva uat on	7 days from n t a	1-60 days from n t a
V s t 3 / Fe ow eye eva uat on (f app cab e)	1-7 days from v s t 2	1-60 days from v s t 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. Should a subject attend for their study 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) or due to a poorly fitting contact lens that can be rectified by ordering a modified contact lens specification, a repeat visit can be conducted a short time later. This visit may involve some or all of the scheduled 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 Initial visit

Subjects should attend wearing their habitual spectacles.

Subjects will 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 history, medical history and contact lens-wearing history of the subject will be noted (including habitual lenses, modality, wear time and comfortable wear time).
2. Auto-keratometry measures will be recorded.
3. The investigator will perform refraction and 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'.
4. Slit lamp biomicroscopy will be carried out for the signs outlined in Table 4 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 (central, superior, temporal, inferior and nasal) as well as an 'overall' grade. The predominant type of corneal staining present will also be recorded.

C ass f cat on	Pr mary s gns	[redacted]
S gns	Con unct va redness L mba redness [redacted] Cornea oedema Cornea sta n ng Locat on of sta n ng Conjunct va sta n ng Pap ary conjunct v t s	[redacted]
Sca e	Efron Grad ng Sca es (scored to nearest 0.1)	Efron Grad ng Sca es (scored to nearest 0.1) (except muc n ba s, where the number s recorded.

Table 4: Biomicroscopic signs. Staining assessed with sodium fluorescein.

The presence of any adverse events will be recorded on the CVI AE form [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.
6. A pair of Biofinity Toric lenses (or a single lens if only one eye is suitable for the study) will be selected from a fitting bank in accordance with the manufacturer's fitting guide, applied and allowed to settle for five minutes.
7. Monocular logMAR visual acuity (high contrast) will be recorded [redacted] and then monocular logMAR visual acuity (high and low

contrast) will be carried out [redacted]

9. Steps 6-8 will then be repeated for the Biofinity sphere lens type.
10. The custom-made Biofinity XR Toric lenses and spherical Biofinity lenses will then be ordered (**Note:** the Biofinity XR Toric lens type will be ordered on the desired cylinder axis and ± 10 degrees of the desired axis to allow lens rotation to be optimised, if required, at visit(s) 2 and 3).
11. The subject will then be discharged and asked to return for Visit 2.

Subjects may wear their habitual lenses between study visits.

3.2.3 Visit 2

Subjects should attend wearing their habitual spectacles. The following procedures will be performed on the randomised eye only, with the fellow eye being patched:

1. Any medical or ocular issues since the last visit will be recorded.
2. The investigator will perform 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. Slit lamp biomicroscopy will be carried out for the signs outlined in Table 4 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 (central, superior, temporal, inferior and nasal) [redacted] The predominant type of corneal staining present will also be recorded.
4. First randomised lens correction (custom-made toric contact lens, spherical contact lens or trial frame correction) will be applied.
5. If a contact lens is applied, allow to settle for five minutes.
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 [redacted]

8. For the Toric contact lens only: If the toric lens is misaligned from its desired orientation by >10 degrees, a new toric lens which compensates for this mis-rotation should be applied and the procedures in steps 4-7 repeated.
9. For the Toric contact lens only: If the investigator is unable to achieve an acceptable toric contact lens fit, but feels that this could be achieved by ordering a new lens specification, the visit should be brought to a premature end (by completion of step 17) and a repeat visit scheduled once the updated custom-made toric lens is available.
10. Fellow eye (non-tested eye) will be covered with an eye patch.
11. Monocular logMAR visual acuity (high and low contrast) will be performed for the first correction type at three different pupil sizes [redacted]. Pupil size will be controlled using a novel, automated room lighting/feedback system.
12. [redacted]
13. Removal of first lens correction and fitting of second randomised correction.
14. The same procedures described above (points 5-13) will be conducted for the second lens correction.
15. The same procedures described above (points 5-13) will be conducted for the third lens correction.
16. [redacted]
17. The investigator will then measure exit VAs and conduct an exit biomicroscopic examination as detailed in section 3.2.2 in accordance with the current Eurolens Research Standard Operating Procedure 'Examination of the anterior segment using slit lamp biomicroscopy'.
18. If only one eye of the subject is to be assessed, payment will be issued and the subject exited from the study.

3.2.4 Visit 3

For those subjects whose second eye is to be assessed. Subjects should attend wearing their habitual spectacles. The following procedures will be performed on the randomised eye only, with the fellow eye being patched:

1. The same procedures as at Visit 2 (3.2.3) will be carried out, for the evaluation of the fellow eye in subjects where both eyes were suitable.
2. 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.

3.2.5 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 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