Clinical investigation plan

C18-649 (EX-MKTG-99)

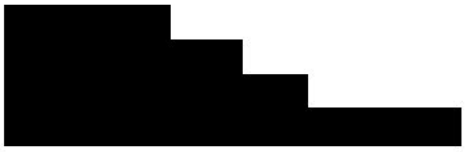
A clinical comparison of two daily disposable soft contact lenses

A clinical evaluation for
CooperVision Inc.

Principal Investigator
Philip Morgan

September 2018

Contents



Study summary

This double-masked, randomised, bilateral crossover dispensing study will compare the clinical performance and subjective acceptance of the PremiO 1day and clariti™ 1 day daily disposable soft contact lenses.

Fifty five subjects will be enrolled on this study and will wear each lens type for one week in random sequence. The following will be assessed throughout the study: [redacted] lens fit, [redacted] and subjective response.

A study summary is shown in Table 1.

Visit	Procedures
Information presentation	On-line explanation of study procedures and visits.
Initial visit	Information and consent forms signed Ocular and contact lens history Medical history [redacted] Application of first lens type [redacted] Lens fit [redacted] assessment Subjective scores Issue study lenses [redacted]
1-week visit	[redacted] Retrieval of unused lenses Subjective scores [redacted] Lens fit [redacted] assessment Lenses removed and discarded [redacted] Fitting of second lens type [redacted] Lens fit [redacted] assessment Subjective scores Issue study lenses [redacted]
2-week visit	[redacted] Retrieval of unused lenses Subjective scores [redacted] Lens fit [redacted] assessment Lenses removed and discarded [redacted] Exit statement signed [redacted]

Table 1: Study summary.

Section 1. Overview

1.1 Background

This project seeks to compare the short-term clinical performance of the PremiO 1day (Menicon Inc), and clariti 1day (CooperVision Inc) daily disposable 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 Philip Morgan PhD MCOptom FAAO FBCLA.

1.3 Study objectives

This study aims to compare the short-term clinical performance of the two contact lenses.

1.4 Study design

This will be a randomised, double-masked, crossover, bilateral dispensing study, controlled by cross-comparison. Fifty-five subjects will wear each lens brand for approximately one week in random order. Lenses will be worn on a daily wear, daily disposable basis.

1.5 Study outcomes

The primary outcome measure of this study will be lens fit. The secondary outcome measure will be vision; and all other measurements will be tertiary outcomes.

1.6 Statistical considerations and power analysis

This work is conducted as a non-inferiority study and as such, the null hypothesis to be tested is that the performance of the clariti 1 day lens is inferior to that of the PremiO 1 day lens.

[redacted], [redacted] and subjective responses 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] Lens fit data are expected to be ordinal data and assessed with non-parametric approaches. 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.

Power analysis was conducted for the following variables using data from a previous study:

- [redacted]
- Vision
- [redacted]

[redacted] A one-sided power analysis for this variable, assuming an alpha of 0.05, a standard deviation of 28.4 units and a meaningful difference of 10 units (on a 100 unit scale) determined that 51 completing subjects would provide 0.80 power. As such, this number of subjects will provide at least 0.80 power for all the variables listed above. To allow for discontinuations, 55 subjects will be recruited.

1.7 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. 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’.

Section 2. Resources

2.1 Subject selection

In this work 55 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 first study 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:

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 between 18 and 40 years of age (inclusive).
2. They understand their rights as a research subject and are willing to sign a Statement of Informed Consent.
3. They are willing and able to follow the protocol.
4. They are an existing silicone hydrogel *reusable* spherical contact lens wearer in both eyes.
5. They have a contact lens spherical prescription between -0.25D and -6.00D (inclusive) based on ocular refraction.
6. They own a wearable pair of spectacles and wear them on the day of the initial visit.
7. At dispensing, they can attain at least 0.20 logMAR distance high contrast visual acuity in each eye with the study lenses within the available power range.
8. They are willing to comply with the wear schedule (at least five days per week and for at least eight hours per day).
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 for 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, or use any rewetting/lubricating drops whilst on this study.
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 contact lens or care system clinical 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 [redacted] 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 ocular adverse event will be reported on CVI report forms and those ocular adverse events 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' ocular 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.

	Lens A	Lens B
Name	PremiO 1 day	clariti 1day
Manufacturer	Menicon Inc.	CooperVision Inc.
Material	Midafilcon A	Somofilcon A
EWC (%)	56	56
BOZR (mm)	8.4	8.6
Diameter (mm)	14.2	14.1
Spherical powers (D)	-0.25 to -6.00 (0.25 steps)	-0.25 to -6.00 (0.25 steps)

Table 2: Study lenses.

2.6.1.1 Use of lenses

The study lenses will be worn on a daily wear, daily disposable basis (i.e. removed at end of day and discarded). Lenses should be worn for a minimum of eight hours per day, five days per week. The lenses are also to be worn for a minimum of two hours before attending the follow-up visits.

2.6.2 Care regimen

No care system will be used on this study.

2.6.3 Inventory control

All study lenses will be provided by CooperVision Inc. All worn lenses will be discarded.

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 and investigators will be masked to the two lenses - lenses will be over-labelled. Masking may be 'broken' if deemed necessary, by the Principal Investigator or Industrial Contact Person.

2.8 Documentation

Documents related to this work that require archiving will be kept by Eurolens Research for a period of 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 as complete when all subjects have signed the exit statement.

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. This study will be performed in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018.

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.

2.13 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 3. Subject management

3.1 Visit scheduling

Subjects will be required to attend three visits. Acceptable date ranges are shown in Table 3.

Visit	Target	Allowable range
Visit 1: Dispensing 1	N/A	N/A
Visit 2:Follow-up & dispensing 2	7 days from Visit 1	6-10 days from Visit 1
Visit 3: Follow-up	7 days from Visit 2	6-10 days from Visit 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 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 initial visit.

At a suitable time, each subject will be asked to watch a short on-line information presentation detailing study visits and procedures. They will be asked to complete several multiple-choice questions to gauge their understanding of the study. Upon successful completion of these questions, the subject will be booked to attend the initial visit. Subjects should be asked not to wear their habitual contact lenses on the day of the study visit.

3.2.2 Visit 1

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

1. Lens handling, application and removal, where necessary.
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 history and contact lens wearing history of the subject will be noted [redacted].
2. Details of general health and medications will be recorded.
3. [redacted]
4. [redacted]
5. [redacted]

[redacted]

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 in the opinion of the investigator, the subject may

be eligible at a later date, the subject may be brought back for up to one repeat visit of this type.

7. The first randomised lens pair [redacted] will be fitted and allowed to settle for five minutes. Subjects will apply the study lenses themselves.
8. [redacted]
9. [redacted]
10. The subject will be asked to score the following with reference to appropriate visual analogue scales (0-100) [redacted]
    - [redacted]
    - Vision
    - [redacted]
    - [redacted]
    - [redacted]
11. [redacted]
12. Lens fit will 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] If the lens is graded as 'unacceptable' (i.e. any of the grades are +2 or -2), the investigator should state why.
13. Subjects will be given a supply of over-labelled contact lenses [redacted]. The subject will then be discharged and asked to return for a one-week follow-up visit wearing the study lenses which need to have been worn for at least two hours. Subjects should be asked to wear their lenses for a minimum of eight hours per day and to wear their lenses every day until the next visit unless he/she experiences symptoms such as redness, discomfort etc. on any given day.

[redacted]

[redacted]

3.2.3 Visit 2 – follow-up 1

Subjects should attend wearing their 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.

1. Any medical or ocular issues since the last visit will be recorded.
2. [redacted]
3. [redacted]
4. Retrieval of any unused lenses.
5. [redacted]
6. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100) [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - Vision
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
7. [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]

[redacted]

8. [redacted]
9. [redacted]
10. [redacted]
11. Lens fit [redacted] assessment, as described in section 3.2.2.
12. The lenses will be removed and discarded.
13. [redacted]
14. The second lens will be fitted and allowed to settle for five minutes.
15. The same procedures as for Visit 1 (section 3.2.2) points 8-14 will be carried out.
16. Subjects will be given a supply of over-labelled contact lenses [redacted].

The subject will then be discharged and asked to return for a one-week follow-up visit wearing the study lenses which need to have been worn for at least two hours. Subjects should be asked to wear their lenses for a minimum of eight hours per day and to wear their lenses every day until the next visit unless he/she experiences symptoms such as redness, discomfort etc. on any given day.

3.2.4 Visit 3 – follow-up 2

Subjects should attend wearing their 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.

Any medical or ocular issues since the last visit will be recorded.

1. [redacted]
2. [redacted]
3. Retrieval of any unused lenses.
4. [redacted]
5. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100) [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - Vision
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
6. [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]

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

7. [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]

11. Lens fit [redacted] assessment, as described in section 3.2.2.
12. The lenses will be removed and discarded.
13. [redacted]

At 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.

[redacted]

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 Industrial Contact Person in order to make comments and ask for re-drafts. If no comments are received from the Industrial Contact Person within eight weeks, a final report will be released with a separate document control page (in duplicate), requesting the Industrial Contact Person to sign both copies, one to keep and the other to be returned to Eurolens Research.

4.2 Disclosure

All matters relating to this clinical study are confidential and should only be disclosed to relevant authorised parties. More precise details relating to disclosure are outlined in the Research Agreement. None of the investigators involved in this work owns equity in the funding company.

4.3 Personnel

[redacted]

Industrial Contact Person

[redacted]