Clinical investigation plan

C16-605 (EX-MKTG-75)

The clinical comparison of the clariti 1 day and DAILIES AquaComfort PLUS daily disposable contact lenses

A clinical evaluation for
CooperVision Inc.

Principal Investigator
[redacted]

May 2019

Contents

Document control

Study title:	The clinical comparison of the clariti 1day and DAILIES AquaComfort Plus daily disposable contact lenses (C16-605) (EX-MKTG-75)
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Study summary

This subject-masked, randomised, bilateral crossover study will compare the clinical performance and subjective acceptance of the clariti 1day soft contact lens with the DAILIES AquaComfort Plus lens when used on a daily wear, daily disposable basis.

Seventy subjects will be enrolled on this study and will wear each lens brand for one week in random sequence. The following will be assessed throughout the study: ocular physiology, [redacted] ocular redness, [redacted] and subjective response.

A study summary is shown in Table 1.

V s t	Procedures
Informat on presentat on	Short on- ne presentat on of study a ms and procedures
D spens ng 1	Informed consent taken Exp anat on of study procedures and sub ect nstruct ons Ocu ar and contact ens h story [redacted] Autokeratometry Ocu ar redness assessment B om croscopy F tt ng of study ens pa r 1 [redacted] Sub ect ve scores Issue study enses and d ary [redacted]
Fo ow-up 1 / D spens ng 2	[redacted] Remova of ens pa r 1 [redacted] Ocu ar redness assessment B om croscopy F tt ng of study ens pa r 2 [redacted]
Fo ow-up 2	[redacted] Remova of ens pa r 2 [redacted] Ocu ar redness assessment B om croscopy [redacted] Ex t form s gned

Table 1: Study summary.

Section 1. Overview

1.1 Background

This project seeks to compare the clinical performance of the clariti 1day lens (CooperVision Inc.) with the DAILIES AquaComfort Plus lens (Alcon Inc.).

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 Michael Read PhD MCOptom FBCLA.

1.3 Study objectives

This study aims to compare the clinical performance of the clariti 1day lens with the DAILIES AquaComfort Plus lens.

1.4 Study design

This will be a randomised, subject-masked, crossover, bilateral study, controlled by cross-comparison. Seventy subjects will use each lens type for a week in random sequence. Follow-up visits for each lens will be performed after one week of wear. Lenses will be worn on a daily wear, daily disposable wear schedule.

1.5 Statistical considerations

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

[redacted] biomicroscopy, ocular redness, [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. Subjective preferences will be compared using chi-squared tests. [redacted] Deviations from this statistical plan will be discussed in the final report. Deviations may be necessary due to differences between the actual data distribution compared with the anticipated data distribution.

1.5.1 Power analysis

Assessment using a dataset from a similar, previous study found that a power of 0.8 or greater is provided by 65 completing subjects for the following measures: subjective comfort at lens dispensing, subjective comfort at the start and end of the day, overall subjective comfort, subjective vision, [redacted] and for the following biomicroscopic signs: conjunctival and limbal redness, corneal staining, conjunctival staining and papillary

conjunctivitis. This analysis assumes a two-tailed paired analysis and an alpha of 0.05. To allow for discontinuations, 70 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. 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 70 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:

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 (18) and capacity to volunteer.
2. They understand their rights as a research subject and are willing and able to sign a Statement of Informed Consent.
3. They are willing and able to follow the protocol.
4. They agree not to participate in other clinical research for the duration of this study.
5. They have a contact lens spherical prescription between -1.00 to - 6.00D (inclusive)
6. They have a maximum of -1.00DC ocular astigmatism in each eye.
7. They can be satisfactorily fitted with the study lens types.
8. 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.
9. They currently use soft contact lenses or have done so in the previous six months.
10. They are willing to comply with the wear schedule (at least five days per week and for at least eight hours per day).
11. 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 ocular abnormality which would, in the opinion of the investigator, normally contraindicate contact lens wear.
9. They have any infectious disease which would, in the opinion of the investigator, contraindicate contact lens wear or pose a risk to study personnel, or they have any immunosuppressive disease (e.g. HIV), or a history of anaphylaxis or severe allergic reaction.
10. They have taken part in any other contact lens or care solution clinical trial or research, within two weeks prior to starting this study.
11. They currently wear either the clariti 1day or the DAILIES AquaComfort Plus lens.

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 [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 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' 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. Device deficiencies will be recorded and reported to the Industrial Contact Person.

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 manufacturers' product instructions.

2.6.1 Lenses

Details of the study lens are provided in Table 2. Both lens types are CE marked. Initial lens selection will be as indicated by the manufacturer fitting guidelines.

	Lens A	Lens B
Name	c ar t 1day	DAILIES AquaComfort P us
Manufacturer	CooperV s on	A con
Mater a	Somof con A	Ne f con A
BOZR (mm)	8.6	8.7
D ameter (mm)	14.1	14.0
Spher ca powers (D)	-0.50 to -6.00 (0.25 steps)	-0.50 to -6.00 (0.25 steps)

Table 2: Study lenses.

2.6.1.1 Use of lenses

Both lens types 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

Clariti 1day lenses will be supplied by CooperVision Inc. DAILIES AquaComfort Plus lenses will be sourced by Eurolens Research. All worn lenses will be discarded. Unworn lenses will be returned to:

[redacted]

2.6.4 Clinical equipment

Clinical equipment is regularly maintained and calibrated as required. Standard operating procedures and international standards are used where appropriate.

2.7 Study control

This study is controlled by cross-comparison. Bias will be minimised by randomising the order of assessment. Subjects will be masked to the two lenses - lenses will be over-labelled. Masking may be 'broken' if deemed necessary, by the Principal Investigator or Industrial Contact Person. Masking will be broken at the end of the Follow-up 2 visit – step 3 (Section 3.2.3), to allow the subject to answer a number of agreement questions relating to the lens brands.

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. Data from paper diaries will be inputted onto an excel spreadsheet, with the paper diaries retained and considered source data.

2.10 [redacted]

2.11 Study completion

The clinical phase of the study will be considered as complete when all subjects have signed the exit statement.

2.12 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.

2.13 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.

2.14 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 – an initial dispensing visit and two follow-up visits, after one week of contact lens wear for each lens type. Acceptable date ranges are shown in Table 3.

Vst	Target	Aowabe range
Dspensng 1	N/A	N/A
Fow-up 1/Dspensng 2	7 days from Dspensng 1	6-10 days from Dspensng 1
Fow-up 2	7 days from Dspensng 2	6-10 days from Dspensng 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-enrollement

Prior to the dispensing visit, 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 Dispensing 1 visit. *Subjects should be asked to attend this visit not having worn their habitual contact lenses on the day of the visit.*

3.2.2 Dispensing 1 visit

The subject will have received a study-specific information form outlining the study at least 24 hours before the consent visit, and will then be required to sign an informed consent form prior to enrolment [redacted] A copy of the signed form will be issued to the subject. When the subject has signed the consent form, they are considered to be enrolled on the study.

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 and medical histories and contact lens-wearing history of the subject will be noted [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. 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	Secondary s gns
S gns	Conjunct va redness L mba redness [redacted] Cornea sta n ng [redacted] Con unct va sta n ng Conjunct va ndentat on Pap ary con unct v t s	B ephar t s Me bom an g and dysfunct on Muc n ba s
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 ocular adverse events will be recorded, and reported as appropriate [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 will be fitted and allowed to settle for five minutes. The subject will be masked to the lens brand.
8. [redacted]
9. [redacted]
10. [redacted]
11. The subject will be asked to score the following subjective scores with reference to appropriate vertical visual analogue scales (0-100) [redacted]
    - Comfort
    - Vision
    - Overall score
12. [redacted]

    Subjects will [redacted] be given a supply of contact lenses which will be over-labelled to maintain masking, for the first study period.

13. [redacted]
14. The subject will then be discharged and asked to return for the one-week follow-up visit wearing the study lenses for at least two hours. Subjects should be asked to wear their lenses for a minimum of eight hours per day, five days per week.

3.2.3 Follow-up 1 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 (any ocular measurement procedures outlined below will be carried out on each eye):

1. Any medical or ocular issues since the last visit will be recorded.
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. The subject will be asked to score the following with reference to appropriate vertical visual analogue scales (0-100) [redacted]
   - Comfort after insertion
   - Comfort before removal
   - Overall comfort
   - Vision
   - [redacted]
   - [redacted]
   - [redacted]
   - Ocular redness
   - [redacted]
   - [redacted]
   - [redacted]
7. [redacted]

[redacted]

8. [redacted]

9. [redacted]

10. [redacted]

11. [redacted]

12. The investigator will then conduct a complete biomicroscopic examination as detailed in section 3.2.1.
13. The second randomised lens pair will be fitted and allowed to settle for five minutes. The subject will be masked to the lenses.
14. The same procedures as for Dispensing 1 (3.2.1) points 8-14 will be carried out.

3.2.4 Follow-up 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.

1. The same procedures as at Follow-up 1 (3.2.2) points 1-12 will be carried out.

2. [redacted]
3. The subject will then be unmasked to the study lens types and the order of wear. [redacted]
4. 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.
5. The subject will be issued with their payment and discharged.

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]