OCULAR TECHNOLOGY GROUP - *International*

BIOFINITY® MULTIFOCAL CONTACT LENSES FITTING METHODS COMPARISON

CLINICAL INVESTIGATIONAL PLAN

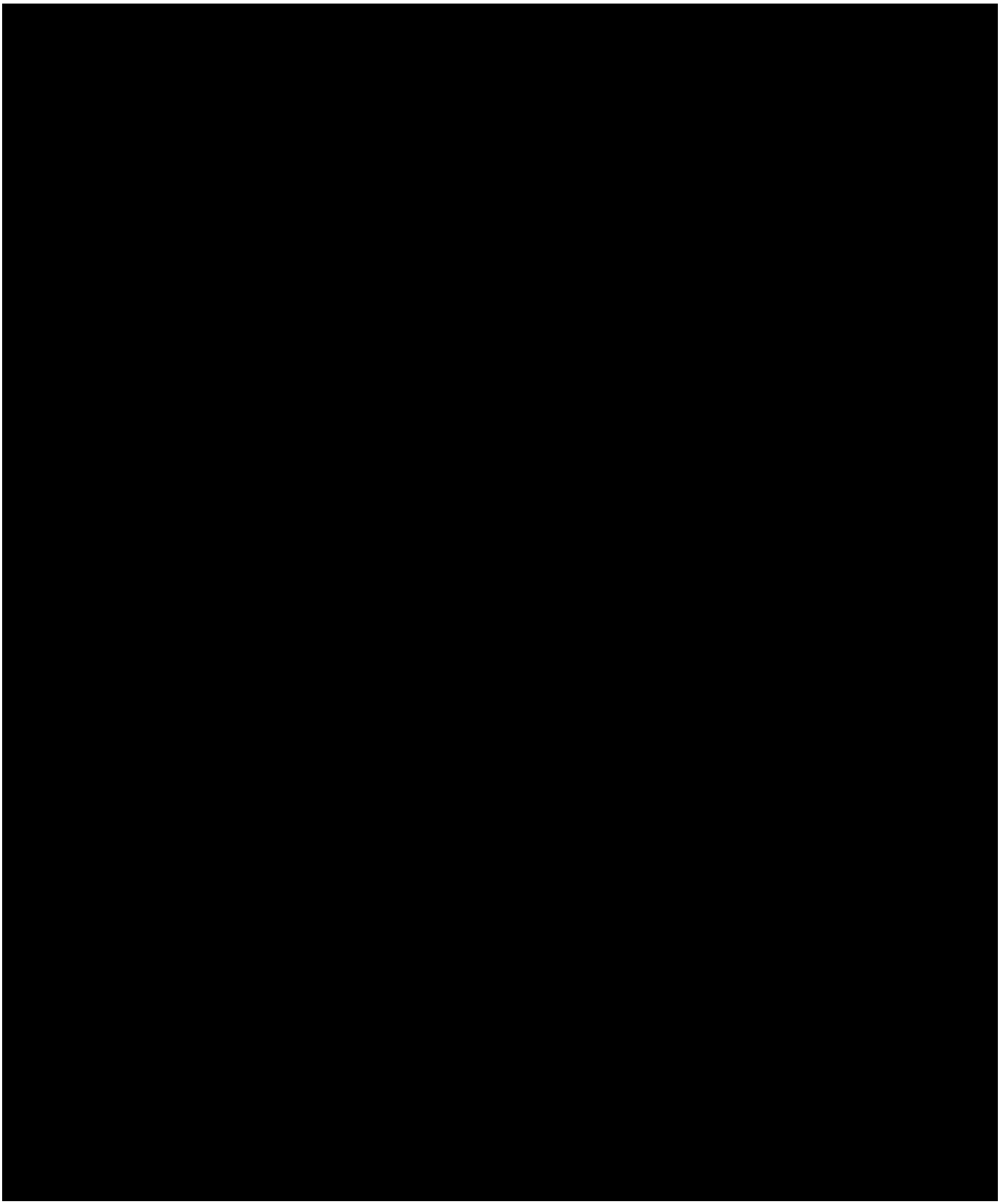
Sponsor:	CooperVision International Limited.
Study Sponsor Number:	CV-22-49
[redacted]	
Version:	1.0
Issue Date:	8th August 2022

[redacted]

[redacted]

DOCUMENT CHANGE HISTORY

Revision	Originator	Description of Change(s)	Date



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1 OVERALL SYNOPSIS

Study Sponsor	CooperVision International Limited
Title of Study	Biofinity® Multifocal Contact Lenses Fitting Methods Comparison
Protocol Number	CV22-19 [redacted]
Type of study	Single arm, prospective, one-week (7 +2/-0 days), cross-over, double masked (participants and research staff carrying out the response measurements), randomised order of testing study.
Study Population	Up to 30 participants will be screened, with the aim to enrol up to 27 with a view to achieve a cohort (participants completing the study as per protocol) sample size of 25 which has been determined to be optimal
Duration of study treatment	Each contact lens types will be worn for one-week (7+2/-0 days) in total the participants will be in the study for up to 18 days.
Inclusion Criteria	In order to be enrolled, each participant shall meet the following criteria: i. At least 40 years old; ii. Have read and understood the Participant Information Sheet; iii. Have read, signed and dated the Informed Consent; iv. Best corrected visual acuity of at least 20/25 in each eye; v. Have normal eyes with the exception of the need for visual correction; vi. Current multifocal contact lens wearer; vii. Spectacle refraction: Distance: Sphere: -6.00D to + 4.00D Astigmatism: 0.00D to -0.75D Near Addition: Established Presbyopes: +1.50D & +1.75D viii. Be willing and able to adhere to the instructions set in the clinical protocol and maintain the appointment schedule.
Exclusion Criteria	The following are specific criteria that exclude a candidate from enrolment in this study: i. Ocular anterior segment infection, inflammation, abnormality, or active disease that would contraindicate contact lens wear; ii. Use of systemic or ocular medications for which contact lens wear could be contraindicated as determined by the investigator; iii. Monocular participants (only one eye with functional vision) or participants fit with only one lens; iv. Any moderate or severe ocular condition observed during the slit-lamp examination at the enrolment visit; v. History of herpetic keratitis, ocular surgery or irregular cornea; vi. Known pregnancy or lactation during the study period; vii. Enrolment of the investigator or his/her staff, family members of the investigator, family members of the investigator's staff, or individuals living in the households of these individuals.
Planned Start Date	15th August 2022
Overall Study Duration	Six months
Objective(s)	The objectives of the study will be to: i. Compare overall vision satisfaction achieved after one week of wear with Biofinity® Multifocal contact lenses fitted in two different manners [redacted]

	ii. [redacted]
[redacted]	[redacted]
Efficacy Endpoint (S)	The primary endpoint will be: i. Overall binocular vision satisfaction after one week of wear; ii. Overall preference after one week of wear. The secondary endpoints will be: i. Mean binocular visual performance measured by timed logMAR mean visual acuity after one week of wear; ii. Number of contact lenses needed per participant to determine the contact lens pair to be dispensed. [redacted]

	vi. [redacted]
[redacted]	[redacted]
Safety Procedure(s)	The procedures to monitor safety will be: i. Identification and prevalence of adverse events; [redacted]

<table>
<tr><td></td><td colspan="3">[redacted]</td></tr>
<tr><td>[redacted]</td><td colspan="3">[redacted]</td></tr>
<tr><td rowspan="2">Experimental Design</td><td>☐ Retrospective
☒ Prospective</td><td colspan="2">☐ Non-Randomized
☒ Randomized (order of testing)</td></tr>
<tr><td>☐ Single masked (participant)
☐ Single masked (investigator)
☒ Double masked*
☐ Sponsor masked
☐ Open label
* Sub-investigators collecting primary and secondary endpoint data and participants will be masked.</td><td colspan="2">☒ Single group
☐ Parallel group
☒ Crossover
☐ Contralateral</td></tr>
<tr><td>Control Product</td><td colspan="3">Biofinity® multifocal CE marked silicone hydrogel contact lenses manufactured from comfilcon A by CooperVision Inc. design +1.50D (control contact lens)</td></tr>
<tr><td>Test Products</td><td colspan="3">Biofinity® multifocal multifocal CE marked silicone hydrogel contact lenses manufactured from stenfilcon A by CooperVision Inc designs +1.50D and +1.50N (test contact lens)</td></tr>
<tr><td>Study Products Use</td><td colspan="3">The study contact lenses will be used as per their CE marking. The contact lenses will be worn on a daily wear basis removed every night, stored overnight in OPTI-FREE® PureMoist® CE marked storage solution and re-inserted the following morning.</td></tr>
<tr><td>Study Visits</td><td colspan="3">Three study visits over a two-week period:
• Visit 1: Screening/Enrolment/Fitting and First Lens Dispensing
• Visit 2 (7 +2/-0 days from Visit 1): First Lens follow up visit, Second Lens Dispensing
• Visit 3 (7 +2/-0 days from Visit 2): Second lens follow up visit/Exit</td></tr>
<tr><td>[redacted]</td><td colspan="3">[redacted]</td></tr>
<tr><td>Regulatory Status</td><td colspan="3">This trial requires Ethics Committee (EC) approval prior to initiation.</td></tr>
<tr><td rowspan="3">Responsibilities</td><td>Sponsor</td><td colspan="2">Name: CooperVision International Limited.
Contact: Dr. Percy Lazon de la Jara</td></tr>
<tr><td>CRO and Data Management</td><td colspan="2">OCULAR TECHNOLOGY GROUP - *International*
Contact: Ned Haigh</td></tr>
<tr><td>Legal Representative (where applicable)</td><td colspan="2">Not Applicable</td></tr>
</table>

2 INTRODUCTION AND RATIONALE

2.1 *Background*

Biofinity® Multifocal CE marked contact lenses are the basis of a well established eight-design multifocal system to correct presbyopia. As for any multifocal contact lenses the performance and acceptance of the vision correction depends in part upon the patient's ocular characteristics leading practitioners to follow different fitting approaches to achieve the best results. [redacted]

The rationale for the study is to compare two common fitting approaches to fit Biofinity® Multifocal contact lenses to assess which one achieves the best results to support proposing that fitting approach for the selection of the first contact lenses to try.

2.2 *Objectives*

The objectives of the study will be to:

i. Compare overall vision satisfaction achieved after one week of wear with Biofinity® Multifocal contact lenses [redacted]

ii. Compare overall preference achieved at the completion of the study with Biofinity® Multifocal contact lenses [redacted]

iii. [redacted]

2.3 *Hypotheses*

The primary hypotheses to be tested will be that:

i. Overall vision satisfaction with Biofinity® Multifocal (Biof MF) contact lens after one week of wear is non-inferior for the test contact lens [redacted]

ii. Overall preference between Biofinity® Multifocal (Biof MF) contact lens is non-inferior for the test contact lens [redacted]

The secondary hypotheses to be tested will be that:

i. Overall binocular visual performance with Biofinity® Multifocal (Biof MF) contact lens after one week of wear is non-inferior for the test contact lens [redacted]

[redacted]

2.4 *Endpoints*

The primary endpoints will be:

i. Overall binocular vision satisfaction after one week of wear;
ii. Overall preference at the completion of the study.

The secondary endpoints will be:

i. Mean binocular visual performance measured by timed logMAR mean visual acuity after one week of wear;
ii. Number of contact lenses needed per participant to determine the contact lens pair to be dispensed.

[redacted]

3 STUDY SPONSOR AND INVESTIGATORS

3.1 *Study Sponsor*

The Sponsor for this investigation will be CooperVision International Limited, Delta Park, Concorde Way, Segensworth North, Fareham, PO15 5RL, UK.

3.2 Clinical Research Organisation

The Clinical Research Organization for this investigation will be OCULAR TECHNOLOGY GROUP - *International* (OTG-*i*) at: Lower Ground Floor, 66 Buckingham Gate, London. SW1E 6AU. United Kingdom.

The study director will be Dr Michel Guillon, PhD, FCOptom, FAAO, FBCLA, CPI Lower Ground Floor, 66 Buckingham Gate, London SW1E 6AU. United Kingdom.

3.3 *Study Site & Investigators*

OCULAR TECHNOLOGY GROUP - International (OTG-i) Clinic at Lower Ground Floor, 66 Buckingham Gate, London SW1E 6AU. United Kingdom.

The study Chief Investigator will be Dr Michel Guillon, PhD, FCOptom, FAAO, FBCLA, CPI and the co-investigator will be Albert Gimenez PGCert.

[redacted]

[redacted]

3.6 *Independent Ethics Committee*

Before clinical study initiation, this protocol, the informed consent form, any other written information given to participants, and any advertisements planned for participant recruitment will be approved by an Independent Ethics Committee (IEC). The Investigator will provide documentation of the IEC approval to the Sponsor. The approval will be dated and will identify the applicable protocol, amendments (if any), informed consent form, all applicable recruiting materials, written information for participants, and participant compensation programs. The IEC will be provided with all information as required by local regulations and/or the IEC. At the end of the study, the Investigator will notify the IEC about the study's completion. The IEC also will be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC on the progress of the study at intervals stipulated by the IEC.

Voluntary informed consent will be obtained from every participant prior to the initiation of any screening or other study-related procedures. The Investigator has a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential participant and the participant must indicate voluntary consent by signing and dating the approved informed consent form. The participant will be provided an opportunity to ask questions to the Investigator, and if required by local regulation, other qualified personnel.

The Investigator will provide the participant with a copy of the consent form written in a language the participant understands. The consent document will meet all applicable local laws and will provide participants with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with participating, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Participants will be told about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The participant also will be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator will keep the original, signed copy of the consent and must provide a duplicate copy to each participant.

The study will be submitted to the IRAS centralized National Research Ethics Service for review. The investigation will not start until approval has been received at the respective site(s).

4 STUDY MATERIAL

4.1 *Introductory Remarks*

The use of the contact lenses in the study will not be associated with a change in patient management / treatment, as all the participants will be current multifocal contact lens wearers.

The study contact lenses will be used as per their CE marking: contact lens fitting will follow the respective fitting guides and the contact lens will be worn daily.

The study contact lenses will be masked to avoid participants' bias as they will use a new pair of contact lenses every day.

4.2 *Study Contact Lenses*

The study contact lenses will be Biofinity® multifocal CE marked silicone hydrogel contact lenses manufactured from comfilcon A by CooperVision Inc [redacted]

The study contact lenses will be worn as per their CE marking on a daily wear basis, the contact lenses will be removed at the end of the day, stored in an approved CE marked contact lens care solution (OPTI-FREE® PureMoist®) and re-inserted the following day.

As per their CE marking the contact lenses can be worn on a daily wear modality up to one month before being replaced [redacted]

5 STUDY POPULATION

5.1 *Recruitment Procedure*

The prospective participants will be selected from the existing clinical populations of the OCULAR TECHNOLOGY GROUP- *International* clinic or via advertising in the local press and/or social media. The participants fulfilling the criteria for inclusion and none of the exclusion criteria will be invited in a sequential manner to participate in the study until the test population is achieved.

The prospective participants from OCULAR TECHNOLOGY GROUP- *International* will initially be contacted by e-mail and if they indicate they are interested in taking part, the investigation will be explained in detail by telephone; if they then confirm their interest, a screening / enrolment / dispensing visit will be scheduled. A copy of the Participant Information Sheet and Informed Consent will be sent to the prospective participants for information at least 24 hours prior to the visit.

The prospective participants responding to the approved advertisement by contacting the clinic via e-mail or telephone and indicating that they are interested in taking part, will be explained the study in detail by telephone; if they then confirm their interest a screening / enrolment / dispensing visit will be scheduled. A copy of the Participant Information Sheet and Informed Consent will be sent to the prospective participants for information at least 24 hours prior to the enrolment visit.

5.2 *Number of Participants*

Up to 30 participants will be screened, with the aim to enrol up to 27 with a view to achieve a cohort (participants completing the study as per protocol) sample size of 25 which has been determined to be optimal, balancing the need for sufficient discrimination and limiting inconvenience to participants by not inflating the study sample (see section 7.1).

Up to 30 participants will be screened with a view to achieving a per protocol population of 25 participants.

Participants will be considered enrolled when they successfully complete the screening visit.

5.3 *Inclusion and Exclusion Criteria*

5.3.1 Inclusion Criteria

There are no requirements as to participant race, gender or occupation.

In order to be enrolled, each participant shall meet the following criteria:

i. At least 40 years old;
ii. Have read and understood the Participant Information Sheet;
iii. Have read, signed and dated the Informed Consent;
iv. Best corrected visual acuity of at least 20/25 in each eye;
v. Have normal eyes with the exception of the need for visual correction;
vi. Current multifocal contact lens wearer;
vii. Spectacle refraction:

Distance:	Sphere:	-6.00D to + 4.00D
	Astigmatism:	0.00D to -0.75D
Near Addition:	Established Presbyopes:	+1.50D & +1.75D

viii. Be willing and able to adhere to the instructions set in the clinical protocol and maintain the appointment schedule.

5.3.2 Exclusion Criteria

To be eligible as a participant, each candidate shall be free of any ocular or medical condition that may affect the results of this study.

The following are specific criteria that exclude a candidate from enrolment in this study:

i. Ocular anterior segment infection, inflammation, abnormality, or active disease that would contraindicate contact lens wear;
ii. Use of systemic or ocular medications for which contact lens wear could be contraindicated as determined by the investigator;
iii. Monocular participants (only one eye with functional vision) or participants fit with only one lens;
iv. Any moderate or severe ocular condition observed during the slit-lamp examination at the enrolment visit;
v. History of herpetic keratitis, ocular surgery or irregular cornea;
vi. Known pregnancy or lactation during the study period;
vii. Enrolment of the investigator or his/her staff, family members of the investigator, family members of the investigator's staff, or individuals living in the households of these individuals.

5.4 *Premature Withdrawal*

A participant will be withdrawn from the investigation before completion if:

i. The participant/parent/guardian withdraws his/her consent to be included in the trial;
ii. An adverse event takes place that is considered by the participant/parent/guardian or the investigator to warrant withdrawal;
iii. Any event that leads the investigator to believe that it is not in the best interest for the participant to continue in the study;
iv. The study is prematurely terminated by the Principal Investigator, local research ethics committee or the Sponsor;
v. The participant is lost to follow-up;
vi. The participant no longer meets the eligibility criteria;
vii. The participant dies.

5.5 *Informed Consent*

Each participant will give written consent according to local IEC requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that will be used will have been approved by both the Sponsor and by the reviewing IEC. The informed consent will be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before entry into the study, the Investigator or an authorised member of the investigational staff will have explained to potential participant the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be informed that if needed their records may be accessed by health authorities and authorised sponsor staff without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations.

The participant will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent will be appropriately recorded by means of the participant's dated signature. After having obtained consent, a copy of the informed consent form will be given to the participant.

6 STUDY DESIGN & PROCEDURES

6.1 *General Description*

The study will be a seven day (7 +2/-0 days), cross-over, order of testing randomised (randomised order between test then control or control then test), double masked (participants and research staff carrying out the response measurements), prospective study. The investigators carrying out the contact lens fitting will not be masked as they will have to carry out the fitting as per the protocol, hence will need to know which design they are using.

The participants will attend a total of three visits and will not take part in any concomitant investigation of any type or take concomitant medications not allowed by the exclusion criteria.

6.2 *Experimental Routine*

Visit 1 – Screening /Enrolment / Baseline / Contact Lens Order 1 Dispensing Visit

Up to 30 potential participants will attend the research clinic for the first visit to initially obtain their informed consent and evaluate their suitability to take part in the investigation. After informed consent has been given, the investigator will review the participant's medical history, ocular history (including concomitant treatments), demographics and contact lens wear history. A series of routine optometric assessments and tests will be conducted to determine the participant's prescription and evaluate the participant's ocular health.

Once it has been verified that the prospective participants meet the inclusion/exclusion criteria they will be enrolled or discharged as applicable. If the participant is eligible, Contact Lens Order 1 fitting and dispensing will be carried out:

- ✓ All study contact lenses will be selected and fitted according to the protocol and fitting guides and the visual acuity [redacted] Modification to the lens power (up to three attempts) to determine the optimal lens powers for the specific contact lens type for the participant will be performed. Participants will wear these contact lenses for a period of approximately 10 minutes in order to adapt to the correction and then distance and near visual acuity will be measured according to the specific requirements, contact lens fitting characteristics will be evaluated. If after 3 attempts, no suitable contact lens can be prescribed, the participant will be discharged from the study.
- ✓ At the conclusion of the visit, if a suitable fit is achieved the participants will be instructed in their use and care and the contact lenses which will be dispensed. The participants will be instructed to wear the study contact lenses for at least 8 hours a day, at least 6 days a week and scheduled for their next study visit in 7 to 9 days.

Visit 2 – Contact Lens Order 1 Follow-up / Contact Lens Order 2 Dispensing Visit
Participants will return for the second study visit after having worn the first study contact lenses for 7 + 2 / -0 days. They will attend the visit wearing the study contact lenses.

The participants medical, ocular, contact lens wearing history and concomitant treatments will once again be reviewed. [redacted] A series of measurements of visual acuity with the study contact lenses will be conducted for distance, intermediate and near as required. Contact lens fitting characteristics will be evaluated, and Order 1 contact lenses will be removed.

Upon removal of the Order 1 study contact lenses the other study contact lens (either test or control based upon the contact lens type used at Order 1) will be inserted and worn for 10 minutes at which time the contact lens fit and vision will be assessed and up to three attempts will be made to determine the optimal correction following the same protocol as during visit 1. If this is not achieved the participant will be discharged from the study, however, if a suitable fit is achieved the participants will be instructed in their use and care and the

contact lenses which will be dispensed. The participants will be instructed to wear the study contact lenses for at least 8 hours a day, at least 6 days a week and scheduled for their next study visit in 7 to 9 days.

Visit 3 – Contact Lens Order 2 Follow-up / Discharge Visit

Participants will return for their last follow-up visit having worn the last study lenses for 7 +2 / -0 days. They will attend the visit wearing the study contact lenses,

The participants medical, ocular, contact lens wearing history and concomitant treatments will once again be reviewed. [redacted] A series of measurements of visual acuity with the study contact lenses will be conducted for distance, intermediate and near as required. Contact lens fitting characteristics will be evaluated, and Order 2 study contact lenses will be removed. Upon contact lens removal and safety evaluation the participants will be discharged from the study.

6.3 *Measures to Avoid Bias*

6.3.1 Randomisation

The order that the two study contact lenses (test and control) will be worn will be randomised to minimise bias. The randomisation scheme will be computer generated using the appropriate software. Upon enrolment, the subjects will be assigned with a participant ID number (sequentially) and this number will be linked to the randomisation assignment.

6.3.2 Masking

The sub-investigators collecting the subjective responses and carrying out the visual performance measurements, which constitute the primary and secondary endpoints, will be masked with respect to the identity of the study contact lenses being worn at each visit. The investigators carrying out the contact lens fitting will not be masked as they will have to follow the test and control contact lenses fitting procedures.

The participants will be masked via overlabelling of the study contact lenses.

6.3.3 Participant Instructions

The participants will be instructed to wear their study contact lenses daily for 7 +2 / -0 days, remove the contact lenses at night (prior to sleep), store the contact lenses overnight in the contact lens care solution supplied for the study and re-insert the contact lenses the following day. A spare pair of masked contact lenses, identifiable by right and left for correct usage, will be supplied to use in case of the breakage or loss of one of the study contact lenses.

Participants will be advised on normal or adaptive symptoms related to contact lens wear. [redacted] These are not reported as adverse events unless in the investigator's opinion they are unexpected in nature, severe or have a high rate of occurrence.

[redacted]

The participants will be instructed to follow standard recommendations provided to contact lens wearers:

i. Avoid rubbing their eyes, always wash their hands prior to touching their eyes or handling their contact lenses, avoid being in a dusty environment and to use sunglasses when they are outdoors.
ii. Exercise care while washing their face with tap water; avoid splashing tap water into the eyes.
iii. Do not swim with contact lenses whenever possible.

iv. Immediately contact the investigator and scheduled to come in for a check-up within 24 hours if their eyes become red, irritated or painful.

[redacted]

6.4 *Procedures*

6.4.1 Endpoint Procedures

The primary efficacy procedures will be:

i. Rating overall vision satisfaction on a 100-point Visual Analog Scale (VAS) at the completion of one week of wear [redacted]

ii. Rating overall preference on a 5-point scale at the completion of the study [redacted]

The secondary efficacy procedures will be:

i. Measurement of mean binocular visual performance by the calculation of the mean visual acuity measured using timed logMAR charts after one week of wear under the following conditions:
   - Distance (at 4 meters) at high luminance (250cd/m^2) with high (90%) contrast chart and low luminance (2.5cd/m^2) with high (90%) contrast chart
   - Intermediate (at 67cm) at medium luminance (50 cd/m^2) with high (90%) contrast chart
   - Near (at 40cm) at medium luminance (50 cd/m^2) with high (90%) contrast chart

ii. Recording of the number of contact lenses needed per eye to determine the contact lens to be dispensed;

[redacted]

6.4.2 Safety Procedures

The procedures to monitor safety will be:

i. Identification and prevalence of adverse events;

ii. Measurement of Snellen / LogMAR visual acuity at distance;

[redacted]

iv. Identification and prevalence of device deficiencies and quality complaints.

[redacted]

[redacted]

6.4.4 Study Management Procedures

The procedures to ensure that the study protocol is followed will be;

i. [redacted]
ii. Study contact lenses fitting as per manufacturer guidelines;

6.5 *Study Visit routine*

The routine below will be followed: The detailed study routine will be as follow:

Visit 1 – Screening, Enrolment and First Study Contact Lens Dispensing Visit

The routine below will be followed:

- Explanation of the study[1]
- Signing of the consent form
- Participant demographics and ocular history questionnaire
- [redacted]
- Standard high contrast Snellen visual acuity at distance and near with sphero-cylindrical and best sphere corrections (monocular & binocular)
- [redacted]
- Review of inclusion and exclusion criteria
- Decision to continue with determination of eligibility
- [redacted]
- ORDER 1 STUDY INITIAL CONTACT LENS INSERTION AND WEAR FOR 10 MINUTES[3,4]
- [redacted]
- Study contact lens prescription suitability evaluation & decision to dispense or change contact lens power[5]
- Standard high contrast Snellen visual acuity at distance and near with and without best sphere over refraction (monocular & binocular)
- ORDER 1 REMOVE INITIAL CONTACT LENS & INSERT ORDER 1 SECOND CONTACT LENS AND WEAR FOR 10 MINUTES[6]
- [redacted]

[redacted]

- [redacted]
- Study contact lens prescription suitability evaluation & decision to dispense or change contact lens power7
- Standard high contrast Snellen visual acuity at distance and near with and without best sphere over refraction (monocular & binocular)
- ORDER 1 REMOVE SECOND CONTACT LENS & INSERT ORDER 1 THIRD CONTACT LENS AND WEAR FOR 10 MINUTES[8]
- [redacted]
- [redacted]
- Study contact lens prescription suitability evaluation & decision to dispense or discharge
- Standard high contrast Snellen visual acuity at distance and near with and without best sphere over refraction (monocular & binocular)
- [redacted]
- [redacted]
- Study product dispensing
- Scheduling

Visit 2 – First Study Contact Lens Follow-up Visit and Second Study Contact Lens Dispensing Visit (7 +2/-0 days after Visit 1)

The routine below will be followed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Standard high contrast Snellen visual at distance and near without over refraction (monocular & binocular)
- Detailed timed logMAR visual acuity without over refraction (monocular & binocular)
- [redacted]
- ORDER 1 CONTACT LENS REMOVAL
- [redacted]
- Standard high contrast Snellen visual at distance and near with sphero-cylindrical correction (monocular & binocular)
- ORDER 2 STUDY <u>INITIAL</u> CONTACT LENS INSERTION AND WEAR FOR 10 MINUTES[10,11]
- [redacted]
- [redacted]
- Study contact lens prescription suitability evaluation & decision to dispense or change contact lens power[12]
- Standard high contrast Snellen visual acuity at distance and near with and without best sphere over refraction (monocular & binocular)

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[7] [redacted]

- ORDER 2 REMOVE INITIAL CONTACT LENS & INSERT ORDER 2 SECOND CONTACT LENS AND WEAR FOR 10 MINUTES[13]
- [redacted]
- [redacted]
- Study contact lens prescription suitability evaluation & decision to dispense or change contact lens power[14]
- Standard high contrast Snellen visual acuity at distance and near with and without best sphere over refraction (monocular & binocular)
- ORDER 2 REMOVE SECOND CONTACT LENS & INSERT ORDER 2 THIRD CONTACT LENS AND WEAR FOR 10 MINUTES[15]
- [redacted]
- [redacted]
- Study contact lens prescription suitability evaluation & decision to dispense or discharge if third contact lens not suitable
- Standard high contrast Snellen visual acuity at distance and habitual near position with and without best sphere over refraction (monocular & binocular)
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Visit 3 – Second Study Contact Lens Follow-up Visit (7 +2/-0 days after Visit 2)

The routine below will be followed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Standard high contrast Snellen visual at distance and near without over refraction (monocular & binocular)
- Detailed timed logMAR visual acuity distance and near without over refraction (monocular & binocular)
- Lens mechanical performance evaluation (subjective rating only)
- ORDER 2 CONTACT LENS REMOVAL
- [redacted]
- Standard high contrast Snellen visual at distance and near with sphero-cylindrical correction (monocular & binocular)
- Overall, [redacted] specific contact lens preference questionnaire
- Discharge

[13] [redacted]

7 SAMPLE SIZE DETERMINATION AND STATISTICAL ANALYSIS

7.1 *Sample Size Determination*

[redacted] Based upon this data sample size estimation has been performed to demonstrate non-inferiority for the test Biofinity® multifocal fitting compared with the control Biofinity® multifocal fitting postulating a true difference of 20% and a margin of equivalence 10%. Calculation based upon a one-sided binomial test with α =0.025, ß = 0.200 gives a minimal samples size of 23 participants.

Based upon the above up to 30 participants will be screened with a view to achieve a per protocol population (PPP) of 25 participants.

Participants will be considered enrolled when they successfully complete the screening visit.

7.2 *Statistical Analysis Plan*

A detailed statistical analysis plan will be developed before database closure.

For all the key parameters recorded, summary tables including descriptive and/or distribution statistics will be given. For continuous and ordinal variables, the following descriptive statistics will be reported: mean, median, standard deviation, minimum, maximum, quartiles and sample size. For ordinal variables, and nominal variables distribution tables will be shown.

[redacted]

A detailed statistical analysis plan will be developed prior to database closure.

8 RISK ANALYSIS

8.1 *Benefits*

There might not be direct benefits to the participants in this study. However, participation in a study may contribute to scientific research information that may be used in the development of contact lens products. In addition, participants will receive an examination of the front part of their eyes and may have the opportunity to try different types of soft multifocal contact lenses at no cost to them.

8.2 *Risks*

All the assessments are routine clinical procedures, and none present any increased risk to participants compared with normal clinical routine.

All participants will be current soft contact lens wearers. The risks of taking part in the study are no greater than those associated with wearing their own contact lenses. The study lenses will be approved marketed soft contact lenses and there will be no lens care system used. The risks associated with wearing the study lenses are similar to wearing any type of approved marketed soft contact lens.

Complications may occur due to non-compliant behaviour. This will be mitigated by the investigator providing the participant with indications for use for the contact lens prior to dispensing. The participants will be under the care of the research investigators for the three weeks study period and the investigators will be present to deal with any unexpected event.

The participants will have their vision checked at the onset of the study and prior to exiting the study to ensure that vision with contact lenses remain unchanged.

[redacted]

[redacted]

9 ADVERSE EVENTS AND REPORTING

9.1 *Adverse Events*

Adverse events including serious adverse events and quality complaints will be reported in accordance with ICH E6 Guideline for Good Clinical Practice. Adverse event reports to the Independent Ethics Committee and MHRA will be made according to their requirements.

9.1.1 Adverse Event Definitions

An 'adverse event' refers to any undesirable clinical occurrence in a participant, whether it is considered to be device-related or not.

Disease signs and symptoms present prior to the study product being utilised are not considered AEs, unless the condition re-appears or worsens in intensity or frequency during the study.

Adverse events (AE) may be classified as 'unanticipated adverse device effects,' 'serious adverse events,' 'significant adverse events,' or 'non-significant adverse events,' as defined below.

Classification	Definition
Serious Adverse Event (SAE)	A SAE is defined in accordance with ISO 14155 as an AE that: a. Led to death b. Led to serious deterioration in the health of the participant, that either resulted in 1. A life-threatening illness or injury, or 2. A permanent impairment of a body structure or a body function, or 3. Inpatient or prolonged hospitalization, or 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c. Led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
Adverse device effect (ADE)	An adverse device effect (ADE) is defined in accordance with ISO 14155 as "an adverse event related to the use of an investigational medical device." This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.
Unanticipated Adverse Device Effect (UADE)	An unanticipated adverse device effect (UADE) is defined in accordance with 21 Code of Federal Regulations (CFR) 812.3 as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."
Serious adverse device effect (SADE)	A serious adverse device effect (SADE) is defined in accordance with ISO 14155 as "an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event."

AE classification, coding (for reporting to the sponsor) and examples are provided in the following table of Contact Lens Adverse Event Classification and Reporting table:

Code	Condition	Potential AE Classification	Reporting
01	Presumed infectious keratitis or infectious corneal ulcer	SERIOUS	Notify sponsor as soon as possible, **within 24 hrs;** Independent Ethics Committee reporting as per requirements
02	Permanent loss of ≥ 2 lines of best spectacle corrected visual acuity (BSCVA)	SERIOUS	
03	Corneal injury that results in permanent opacification within central cornea (6mm)	SERIOUS	
04	Uveitis or Iritis (e.g. presence of anterior segment inflammation as described in ISO 11980, Annex B)	SERIOUS	
05	Endophthalmitis	SERIOUS	
06	Hyphema	SERIOUS	
07	Hypopyon	SERIOUS	
08	Neovascularization within the central 6mm of cornea	SERIOUS	
00	Other serious event	SERIOUS	
11	Peripheral (outside central 6mm), non-progressive, non-infectious ulcer	SIGNIFICANT	Notify sponsor as soon as possible, **within 5 working days**; Independent Ethics Committee reporting as per requirements
12	Symptomatic corneal infiltrative event	SIGNIFICANT	
13	Superior epithelial arcuate lesions (SEALs) involving epithelial split	SIGNIFICANT	
14	Corneal staining ≥ dense coalescent staining up to 2mm in diameter (e.g. moderate, ISO 11980 grade 3)	SIGNIFICANT	
15	Corneal neovascularization ≥ 1.0mm vessel penetration (e.g. ≥ ISO 111980 Grade 2), if 2 grade change from baseline	SIGNIFICANT	
16	Any temporary loss of ≥ 2 lines BSCVA for ≥ 2wks	SIGNIFICANT	
17	Any sign and/or symptom for which participant is administered therapeutic treatment or which necessitates discontinuation of lens wear for ≥ 2 weeks	SIGNIFICANT	
10	Other significant event	SIGNIFICANT	
21	Conjunctivitis (bacterial, viral or allergic)	NON-SIGNIFICANT	
22	Papillary conjunctivitis if ≥ mild scattered papillae/follicles approximately 1mm in diameter (e.g. ISO 11890 Grade 2), if 2 grade change from baseline	NON-SIGNIFICANT	
23	Asymptomatic corneal infiltrative events	NON-SIGNIFICANT	
24	Any sign and/or symptom for which temporary lens discontinuation for > 1 day is recommended (if not already classified)	NON-SIGNIFICANT	
20	Other sign and/or symptom warranting classification as a non-significant adverse event	NON-SIGNIFICANT	

9.1.2 Normal or Adaptive Symptoms

Transient symptoms such as end-of-day dryness, lens awareness, itching or burning or other discomfort may occur with contact lens wear and may occasionally reduce wearing time. These are not reported as adverse events unless in the investigator's opinion they are unexpected in nature, severe or have a high rate of occurrence.

This clinical study will also ascertain satisfaction or preference with participative attributes such as comfort, vision, or lens handling. Responses to these participative questionnaires will not be considered as Adverse Events, complaints or Device Malfunctions.

9.1.3 Procedures for Adverse Events

Treatment of an adverse event will depend on its nature and severity. Based on the clinical judgment of the investigator the participant may be referred to an ophthalmologist for treatment. The investigator will attempt to determine whether the reaction is related to the contact lenses or a result of other factors. An Adverse Event Form will be completed for each adverse event. If both eyes are involved, each eye will be counted as one adverse event and Adverse Event information will be completed for each eye. Whenever possible, the adverse event will be photo-documented.

Expenses incurred for medical treatment as part of study participation will be paid by the sponsor (bills and prescription receipts kept). The participant must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.

9.2 *Reporting Adverse Events*

All potential Serious and Unanticipated Adverse Device Effects that are related or possibly related to participation will be reported to the Principal Investigator and the sponsor within 24 hours of the investigator becoming aware of the event. The Principal Investigator will report the event to the Ethics Committee as soon as possible (by fax, mail/delivery, phone, or email) following the site Independent Ethics Committee guidelines. All fatal or life-threatening events will be reported immediately to the Independent Ethics Committee.

Significant and Non-Significant Adverse Events will be reported to the sponsor using the Adverse Event notification form as soon as possible, but no later than 5 working days after the occurrence.

[redacted]

10 DEVICE DEFICIENCIES

Device deficiencies are defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: This definition includes malfunctions, use errors, and inadequate labelling.

11 INVESTIGATOR, SPONSOR AND MEDICAL MONITOR RESPONSIBILITIES

11.1 *Investigator Responsibilities*

The investigator is responsible for ensuring participant safety and data quality by: protocol compliance, adherence to GCP and local regulatory requirements, and the Declaration of Helsinki. The investigator must ensure that he/she is appropriately qualified and legally entitled to practice and is trained in the proper method of obtaining informed consent.

The investigator must have the appropriate resources to conduct the clinical trial, be familiar with the protocol and agree to adhere to it, support monitoring and auditing activities, communicate with the Sponsor regarding any clinical trial issues or need for protocol modifications, make the necessary arrangements to ensure proper conduct and completion of the clinical trial, and ensure the protection and welfare of the participant, including arranging any emergency treatment as needed.

The investigator must ensure written Independent Ethics Committee approval is received prior to the start of the clinical trial, that the Ethics Committee and sponsor is kept informed of the clinical trial progress, including serious/adverse events and deviations as required by them, and that any changes to the protocol are notified to the Ethics Committee and review written approval prior to implementation.

The investigator must ensure that the study is posted on ISRCTN public website prior to enrolling any participant.

The investigator must try to ensure adequate participant recruitment; that all necessary and appropriate information is given to potential participants to ensure informed consent; is taken and documented; and that clinical records indicate the participant is enrolled in a clinical trial. The investigator must ensure that participants are provided with emergency contact details along with a procedure to follow in the case of an emergency, and that participants are kept informed as pertinent new information becomes available that may affect their decision to participate.

The investigator has primary responsibility for the accuracy, legibility and security of all clinical investigation data, video recordings, documents and participant records at the Investigator site during and after the clinical trial. CRFs are to be signed by the investigator, and any alterations to data are to be made by authorized personnel, initialled and dated by name or, in the instance of electronic data, an audit trail will be in place, with no obstruction of the original data.

The investigator must ensure that data be kept for the minimum time as specified by this protocol. The test product must be accounted for (the quantity of the devices received must be reconciled with the quantities of the device used, discarded or returned), and must also be responsible for the supervision and assignment of duties to all responsible for the conduct and evaluation of the clinical trial for the Investigator centre involved.

11.2 *Sponsor Responsibilities*

The Sponsor has delegated the selection of the Investigator and study site to the CRO, who should also select and appoint a monitor. The Sponsor has the ultimate responsibility for monitoring. The Sponsor is to supply and keep an up-to-date signed protocol and protocol amendments.

The sponsor should ensure appropriate information is provided to the Investigators to conduct the clinical trial; that deviations are reviewed with the Investigator as needed and included in the final report. Adverse events are reported by the investigator, and the sponsor in turn will then notify their applicable regulatory authorities, and other investigators as appropriate. The Sponsor is to maintain Sponsor-specific clinical trial documentation as required by the regulatory authorities and to ensure the investigator is aware of their record keeping responsibilities.

11.3 *Medical Monitor Responsibilities*

The Medical Monitor will be a physician specializing in ophthalmology. To reduce study bias concerns, the Medical Monitor will not have any real or potential conflict of interest with the Sponsor, Study Investigator or participating Investigative site.

The primary purpose of the Medical Monitor is to ensure an independent review all Serious Adverse Events (SAE), device-related Adverse Events and AE related to the safety endpoints. When reviewing SAE and device-related adverse events, the Medical Monitor will report the relationship between the AE and the study device and the study procedure. The results of all events reviewed by the Medical Monitor will be documented.

The Medical Monitor for the OTG-i Research Clinic will be Ali A. Mearza MB BS, FRCOphth, who is contracted to OTG-i Research Clinic for this activity.

12 GENERAL CLINICAL MANAGEMENT

12.1 *Data Recording*

The clinical data will be recorded on dedicated electronic case report forms (eCRFs) specifically designed to match the testing routine for each visit. Entrypoint 16 (Phoenix Software International), will be used for data recording. All data captured with this software will be stored in a secure SQL database. The eCRFs will be reviewed for accuracy and comprehensiveness once completed and signed by the investigator. A summary of the data will also be recorded in the participants' clinical records. These constitute the participants' source documents, which will be signed by the investigator. The content and structure of the eCRFs are compliant with ISO14155:2011.

12.2 *Clinical Monitoring*

OCULAR TECHNOLOGY GROUP - International will monitor the study in a manner consistent with ICH GCP E6, EN ISO 14155:2011 and the Declaration of Helsinki. The study monitor will maintain close contact with the Principal Investigator and the Investigator's designated staff. The monitor's responsibilities will include:

i. Ensuring that the investigation is being conducted according to the protocol;
ii. Ensuring the rights and wellbeing of participants are protected;
iii. Ensuring that protocol deviations are documented with corrective action plans, as applicable;
iv. Clarifying questions regarding the study;
v. Resolving study issues or problems that may arise;
vi. Reviewing the study records to ensure completeness and accuracy;
vii. Study and participant source document records reviewed will include:
    a. The Information and Consent Form
    b. Source documentation including consenting, medical history, concomitant medications and adverse event information as applicable.
    c. Study related Regulatory documents as per ICH E3 section 8

The clinical monitor will review study data and will perform, at a minimum, one Interim and one Close-Out Visit on site.

12.3 *Study Product Accounting*

Study product records include the study contact lens shipping orders, dispensing logs and the physical count and disposition of the remaining unused study contact lenses. Used worn lenses collected at the study visits will be discarded by the study site personnel. The clinical monitor will ensure product is reconciled and any discrepancies are investigated and either corrected or documented. At study conclusion all study contact lenses will be reconciled.

12.4 *Participant Compliance Monitoring*

Throughout the course of the study the clinical monitor will review study data for participant compliance to the protocol. Non-compliances will be documented as protocol deviation(s). If a deviation is determined to be major, the deviation will be reported to the Ethics Committee as per their requirements.

12.5 *Unmasking of Study Information*

Masked information on the identity of the assigned study product(s) should not be disclosed during the study unless there are medical or safety reasons to do so, for example knowledge of the product may be necessary for the treatment of some adverse advents. The randomisation and masking data is under the control of a

designated unmasked member of staff. In the event of any adverse event requiring unmasking, the identity of the product can be requested by the Investigator, Medical Monitor or any medical personnel. In the event that unmasking occurs, the following should be recorded:

i. The ID of the unmasked participant,
ii. The reason for unmasking,
iii. The study staff person responsible for unmasking,
iv. A list of person(s) who have been unmasked.

13 ADMINISTRATIVE MANAGEMENT

13.1 *Relevant Standards*

This clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline, the International Standards Organization (ISO) Clinical investigation of medical devices for human participants – Good clinical practice (ISO 14155:2011(E)), Ophthalmic optics – Contact lenses and contact lens care products – Guidance for clinical investigations (ISO 19980:2012 (E)) and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

13.2 *Deviations from the Protocol*

Protocol deviations are unanticipated or unintentional changes to a study after it has received prior sponsor approval and ethics clearance. Protocol deviations can be major or minor.

If the deviation affects participant's rights, safety and wellbeing, or the scientific integrity of the clinical investigation, the ethics committee must be contacted with requests for deviations, and reports of deviations. Under emergency circumstances, deviations from the clinical investigational plan to protect the rights, safety and well-being of participants may proceed without prior approval of the sponsor and the ethics committee. Such deviations shall be documented and reported to the sponsor and the ethics committee as soon as possible.

13.2.1 Major Protocol Deviations

Major protocol deviations may impact the research protocol, information consent document or other study materials, usually cannot be anticipated ahead of time and are often necessary to ensure the safety and welfare of the participants.
The following are examples of protocol deviations that must be reported to the EC and MHRA:

i. Changes in procedures initiated to eliminate immediate risks/hazards to participants;
ii. Enrolment of participants outside the protocol inclusion/exclusion criteria whether agreed to or not by the sponsor;
iii. Inadvertent deviation in specific research intervention procedures or timing of the research intervention which could impact upon the safety or efficacy of the study-related intervention or upon the experimental design;
iv. Information consent documentation violations: no documentation of informed consent; incorrect version of, or incomplete, informed consent documentation used.

13.2.2 Minor Protocol Deviations

Protocol deviations caused by or which originate with research participants are generally considered minor, and normally are not reported to the Independent Ethics Committee unless these result in increased risk to the participants). The following are examples of protocol deviations that are considered minor and do not require reporting to the Independent Ethics Committee and MHRA:

i. Logistical or administrative aspects of the study (e.g., study participant missed appointment, change in appointment date);
ii. Inadvertent deviation in specific research intervention procedures or timing of the research intervention which would *not* impact upon the safety or efficacy of the study-related intervention or upon the

experimental design (i.e., missing a measurement during a session that is not considered critical for the study).

13.3 *Modifications to the Clinical Investigational Plan*

Any modifications to the clinical investigational plan that are considered necessary can only be effected after approval from the principal investigator and the Independent Ethics Committee. In an emergency situation, as indicated in ISO14155, the clinical investigator will exercise his judgement to safeguard the participant's interest and may deviate from the clinical investigation plan without the prior approval of the Independent Ethics Committee. In that case, the deviation will not be considered as a breach of agreement but will be reported to the ethics committee.

13.4 *Termination of the Study*

The Sponsors reserve the right to terminate the study at any time for any reason. The principal investigator has the discretion to initiate stopping the study based on participant safety or if information indicates the study's results may be compromised. The Investigator should promptly notify the IEC of the termination or suspension and of the study and the reason.

13.5 *Data Protection*

All information obtained during the course of the investigation will be regarded as confidential and will be handled in accordance with the Data Protection Act and the General Data Protection Regulation (GDPR) guidelines. All personal data gathered in this trial will be treated in strictest confidence by investigators, monitors, OTG-*i* personnel, the sponsor and the independent ethics committee. No data will be disclosed to any third party without the express permission of the participant concerned, with the exception of OTG-*i* personnel (monitor, auditor), the sponsor, the independent ethics committees and regulatory organisations in the context of their investigation related activities which, as part of the investigation will have access to the CRFs and source documents.

13.6 *Data Handling and Record Keeping*

The data analysis will be carried out by OTG-*i*.

All records, including CRFs, will be kept in the files of the Principal Investigator site for the latter of the two dates a period of two years after the date on which the investigation is terminated or completed, or the date that the records are no longer required for legal clinical requirements.

13.7 *Reporting*

OTG-*i* shall submit a final report to the sponsor as per the terms in the Statement of Work.

OTG-*i* shall also submit a summary one-year update and/or a summary final report to the Independent Ethics Committee.

OTG-*i* shall also submit a summary final report to be posted on the public website ISRCTN.

13.8 *Publication Policy*

The study data will be wholly owned by the Sponsor. The results of the study may not be used in publications or presentations without the written permission of the Sponsor.

13.9 *Compensation*

The Sponsor will compensate the Contract Research Organisation for work carried out as agreed prior to the study and will supply or pay for consumables for use in the study as detailed in the contract.

13.10 *Indemnity/Insurance*

The Sponsor will take out indemnity to cover the participants and research staff involved in the study and the ethics committee. This will NOT cover the research staff for clinical negligence. Investigators will have their own professional indemnity.