VISIONCARE RESEARCH

PROTOCOL

VERSION 1.0

AN EVALUATION OF THE FITTING SUCCESS RATE OF SENOFILCON A SOFT CONTACT LENSES IN THREE DESIGNS

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An Evaluation of the Fitting Success Rate of Senofilcon A Soft Contact Lenses

(TRTN-501)

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An Evaluation of the Fitting Success Rate of Senofilcon A Soft Contact Lenses

(TRTN-501)

SYNOPSIS

TITLE: An evaluation of the fitting success rate of senofilcon A soft contact lenses.

STUDY OBJECTIVES:

1. To compare the lens fitting success rates for three combinations of senofilcon A lens pairs when fitted to a population skewed to larger corneas.
2. To compare the actual fitting success rates of senofilcon A lenses with theoretical values from the Young model.
3. To compare the fitting characteristics of senofilcon A lenses (tightness, corneal overlap) with theoretical values from the Young model.

STUDY DESIGN: This will be an approx. 40-60 subject, one-day, double-masked, randomised, repeated measures study. Each subject will wear the three lens types bilaterally in random succession (Acuvue® OASYS® with Hydraclear Plus™ in two base curves and Acuvue® 1·Day Oasys with HydraLuxe™ in one base curve). A total of six lenses will therefore be worn by each subject (3 per eye).

HYPOTHESES:

i. The fitting success rate for a combination of two senofilcon A designs is greater than for a single design when fitted to a population skewed to larger corneas.

ii. The fitting success rates for senofilcon A designs are equivalent to those predicted by the Young model.

iii. The fitting characteristics (tightness, corneal overlap) for senofilcon A designs are equivalent to those predicted by the Young model.

TEST PRODUCTS: Both lens types are manufactured by JJVC, in senofilcon A material with 38% water content and a shrinkage factor (20→34ºC) of 0.997. Both are available in powers -1.00 to -6.00D and are CE marked.

- Acuvue® 1·Day Oasys with HydraLuxe™ (8.50/14.3)
- Acuvue® OASYS® with Hydraclear Plus™ (8.40/14.0, 8.80/14.0)

LENS CARE PRODUCTS: Unpreserved saline for rinsing, e.g. Sauflon saline.

NO. SUBJECTS: Approximately 40-60 subjects. An attempt will be made to include ~50% subjects who have an HVID >11.75mm or corneal diameter >13.75mm.

STUDY POPULATION: Volunteer subjects will be enrolled if they meet the baseline screening criteria and the inclusion and exclusion listed below. Ideally at least half of the eyes will fall within the top quartile of average corneal diameters ie >HVID 11.75mm or corneal diameter >13.75mm or will have demonstrated loose / tight fitting contact lenses in previous studies.

Inclusion Criteria:

i. Age 18-70 years.
ii. Able to read, comprehend and sign an informed consent.
iii. Willing to comply with the wear and study assessment schedule.
iv. Spherical distance prescription between -0.50 and -6.00 (inc.).
v. Astigmatism, if present,≤1.50DC in both eyes.
vi. Have normal eyes with no evidence of any ocular abnormality or disease. For the purposes of this study a normal eye is defined as one having:

- A clear central cornea
- No anterior segment disorders
- No clinically significant slit lamp findings (i.e. corneal oedema, significant staining, central scarring, infiltrates, active neovascularisation)
- No other active ocular disease (including pterygia)

Exclusion Criteria:

i. Previous anterior ocular surgery
ii. Any active corneal infection, injury or inflammation
iii. Large pinguecula likely to affect soft lens fit
iv. Systemic or ocular disease or medication which might interfere with CL wear
v. Pregnancy or breastfeeding
vi. Participation in any concurrent trial

NO. SITES: Two sites in UK: Visioncare Research Ltd, Farnham; Aston Research Clinic, Birmingham

END POINTS: Completion of assessment of three pairs of lenses or discontinuation.

VISITS/SCHEDULE: One visit

PROCEDURE: Lenses will be inserted and each pair assessed after ~30 minutes.

CLINICAL VARIABLES: **Primary variables:**

Lens fit: horizontal* & vertical* centration (mm), post-blink movement in primary gaze* (mm), version lag (mm), edge tightness (0-4), tightness (push-up %), horizontal corneal overlap (mm)*, diameter acceptance (mm), overall fit acceptability (0-5), fit success rate (%).

Corneal topography: Sim-K-readings and corneal shape factor (Medmont), horizontal HVID* (photo slit lamp) corneal sagittal height, corneal diameter (Visante OCT).

* From photographs / video

THEORETICAL FIT VARIABLES: Edge strain (%), corneal overlap (mm), fit success (Yes/No) based on following criteria: Edge strain: 0-6%, Horizontal corneal overlap: 0.2-1.2mm.

1 INTRODUCTION

Since ocular topographies vary within the population,[1] it is important that contact lens designs are selected that comfortably and successfully fit a wide range of eyes. Multiple designs generally give a wider coverage of the population than single designs. Because soft contact lenses are generally not available in a wide range of parameters, it is difficult to evaluate the effectiveness of design combinations. However, senofilcon A lenses have recently become available in multiple diameters, which offers the opportunity to explore the utility of various design combinations.

Computer modelling provides useful insights into the relationship between lens design and fit and allows an estimation of the fitting success rate for a given lens design on a given population.[2,3] Recent calculations suggest that a combination of multiple diameter designs is likely to be more successful than multiple base curves of identical lens diameter.[4]

The main purpose of this study is to evaluate the fitting success of various combinations of senofilcon A lens designs. A secondary purpose will be to evaluate the validity of the Young soft contact lens fit model.[2]

2 STUDY OBJECTIVES

i. To compare the lens fitting success rates for three combinations of senofilcon A lens pairs when fitted to a population skewed to larger corneas.

ii. To compare the actual fitting success rates of senofilcon A lenses with theoretical values from the Young model.[2]

iii. To compare the fitting characteristics of senofilcon A lenses (tightness, corneal overlap) with theoretical values from the Young model.

2.1 Hypotheses

The following hypotheses will be tested:

i. The fitting success rate for a combination of two senofilcon A designs is greater than for a single design when fitted to a population skewed to larger corneas.

ii. The fitting success rates for senofilcon A designs are equivalent to those predicted by the Young model.

iii. The fitting characteristics (tightness, corneal overlap) for senofilcon A designs are equivalent to those predicted by the Young model.

3 STUDY DESIGN & RATIONALE

This will be a one-day, double-masked, randomised, repeated measures study. Each subject will wear the three lens types (Acuvue® OASYS® with Hydraclear Plus™ in two base curves and 1·Day Oasys with HydraLuxe™ in one base curve). A total of six lenses will therefore be worn by each subject (3 per eye).

An attempt will be made to include subjects who have large corneas or have previously demonstrated loose / tight fitting contact lenses since eyes with larger corneas tend to be less successful in contact lens fitting.

3.1 Randomisation

Subjects will wear each of the three lens types bilaterally in random succession. A random number generator (Microsoft Excel) will determine the randomisation of lenses to subjects, which is then incorporated into the Randomisation Log.

The randomised assignment of subjects will be performed at the first assessment prior to the first randomised lens fitting. The following must be ensured prior to randomisation:

- Informed consent has been obtained
- Subjects meet all inclusion / exclusion criteria
- Subject history and baseline information have been collected

Subjects who are discontinued may be replaced in order to achieve the targeted minimum number of cohort subjects, but the ID number will not be reused.

3.2 Masking

To prevent bias, subjects will be masked to lens type and lens codes, and investigators will be masked to lens code. An unmasked individual at Visioncare Research will be responsible for preparing the lenses by over-labelling with the appropriate code. The lenses will be coded (A, B or C) to facilitate masking.

4 INVESTIGATIONAL SITES

4.1 Number of Sites

Two investigational sites in the UK: Visioncare Research Clinic, Farnham: Aston University Research Clinic, Birmingham

4.2 Investigator Recruitment

The Investigators will be required to fulfil the following criteria:

- General Optical Council (GOC) registered optometrist
- At least two years post-registration contact lens fitting experience
- Experienced investigators trained in Good Clinical Practice (GCP)
- Willingness to follow the study protocol and to co-operate with the study monitors

5 STUDY POPULATION

5.1 Number of Subjects

Approx. 50 subjects (40-60 subjects) who fulfil the inclusion criteria will be fitted with study contact lenses.

In order to fully explore the hypothesis an attempt will be made to include subjects who have an HVID of >11.75mm, Corneal Diameter of >13.75mm, or who have exhibited ‘loose’ or ‘tight’ lens fittings in previous studies.

5.2 Inclusion Criteria

All subjects must satisfy the following conditions prior to enrolling in the study:

i. Age 18-70 years.

ii. Able to read, comprehend and sign an informed consent.

iii. Willing to comply with the wear and study assessment schedule.

iv. Spherical distance contact lens requirement between -0.50 and -6.00 (inclusive).

v. Astigmatism, if present, ≤1.50DC in both eyes.

vi. Have normal eyes with no evidence of any ocular abnormality or disease. For the purposes of this study a normal eye is defined as one having:

- A clear central cornea
- No anterior segment disorders
- No clinically significant slit lamp findings (i.e. corneal oedema, staining, central scarring, infiltrates, active neovascularisation)
- No other active ocular disease (including pterygia)

5.3 Exclusion Criteria

Any of the following will render a subject ineligible for inclusion:

vii. Previous anterior ocular surgery

viii. Any active corneal infection, injury or inflammation

ix. Large pinguecula likely to affect soft lens fit

x. Systemic or ocular disease or medication which might interfere with CL wear

xi. Pregnancy or breastfeeding

xii. Participation in any concurrent trial

5.4 Subject Identification

Subjects will be identified by a six-digit code made up of the site identifier (XX), the two-digit subject enrolment number (XX), and subject initials (XX). Enrolment numbers 01-30 will be assigned to Site 1, and numbers 31-60 will be assigned to Site 2.

The enrolment ID **must** be assigned to the subjects sequentially. Enrolment numbers will be in ascending order for each site. Thus, the first subject to be enrolled at Site 01 will be 01/01, the second 01/02 and so forth. The first subject to be enrolled at Site 2 will be 02/31, the second 02/32 and so on.

5.5 Study Withdrawal Criteria

Due to the nature and duration of the study, no circumstances are foreseen whereby this study would be prematurely terminated. However, if during the study it becomes evident to the Investigator that the study contact lenses pose a threat to subject well-being, the study will be terminated. The Research Ethics Committee (REC) will be advised of the reason for termination.

5.6 Subject Replacement

Subject IDs will not be reused should a subject drop-out or be discontinued from the study. If subjects are discontinued or drop out of the study, new subjects may be enrolled to ensure adequate subject numbers complete the study.

5.7 Subject Compliance

This is a one-day study and, therefore, there is little scope for subject non-compliance. However, subjects will be questioned at the follow-up assessments to check whether they have removed the lenses or failed to follow the instructions for any reason.

6 MATERIALS

6.1 Study Lenses

Table 1: Lens Details

	Acuvue® 1·Day Oasys with HydraLuxe ™	**Acuvue® OASYS® with Hydraclear Plus ™**
Manufacturer	JJVC	JJVC
Material/ water	senofilcon A	senofilcon A
Water content	38%	38%
Shrinkage factor (20→34ºC)	0.997	0.997
Base curve (mm)	8.50	8.40, 8.80
Diameter (mm)	14.3	14.0
Powers (D)	-1.00 to -6.00	
	CE marked	

6.2 Trial Lens Fitting Sets

Lenses will be provided by the Investigator sites.

6.3 Lens Care Products and Other Study Products

Unpreserved saline for rinsing away fluorescein or for rinsing contact lenses, e.g. Sauflon saline.

6.4 Lens Preparation

An unmasked individual at Visioncare Research will be responsible for preparing the lenses by over-labelling with the appropriate code: A, B or C.

6.5 Lens Replacement Schedule

Subjects will wear a new pair of lenses for the duration of each 30-minute section of the study. Therefore, there is no requirement for subjects to replace their lenses. If subjects experience any complications with the study lenses, they should speak to the Investigator.

6.6 Product Accountability

Product Accountability and Dispensing Foil Logs will be kept by each site (Appendix 3 and 4). Number of lenses received (listed by power and lot number) and number of lenses used (even if not dispensed) will be recorded on these logs.

6.7 Study Document and Case Report Forms (CRFs)

The following forms will be completed where appropriate:

Investigator CRF Booklet:
A) Baseline form
B) Lens Assignment Form
C) Follow Up Assessment form (including any Unscheduled Visits)
D) Study Exit Form

Additional Forms
A) Statement of Informed Consent
B) Participant Information Sheet
C) Eligibility Checklist (in Baseline CRF)
D) Enrolment Log
E) Randomisation Log
F) Adverse Event Form
G) Product Accountability Log
H) Product Dispensing Foil Log

7 TREATMENT

7.1 Study Product Formulations

The contact lenses are CE marked and supplied sterile in single use blister packs containing buffered saline solution.

7.2 Device Administration

The single use devices will be used on a daily wear basis and disposed of after fitting and assessment on same study day.

8 METHODS AND ASSESSMENTS

8.1 Subject Recruitment

Recruitment materials (adverts, letters, etc.) must be approved by the Research Ethics Committee. The Investigator will provide an approved advert and letter for the recruitment purposes. Any changes to these must be submitted back to the ethics committee.

The procedures listed below will be conducted on all subjects. Variables must be collected in the order they are listed on the Case Report Form (CRF).

To participate in this clinical study, the Investigator will explain the Statement of Informed Consent to the subject, ensure each subject understands the Participant Information Guide and determine subject eligibility.

The Investigator is required to answer any questions the subject has concerning the study or the information contained in the Statement of Informed Consent and Participant Information Guide.

A subject is considered enrolled when he or she signs the Statement of Informed Consent.

8.2 Study Visits

8.2.1 Visit Schedule

This will be a non-dispensing study. Each subject will be required to attend one scheduled study visit over a period of approximately 3.5 hours in a single day. They will be examined at three different time-points.

First Time-point:

Screening and Enrolment:

Baseline Assessment:

1st Pair Study Lens Assessment:	Insert 1st pair of study lenses, assess fit after 30 minutes then discard lenses

Second Time-point:

2nd Pair Study Lens Assessment:	Insert 2nd pair of study lenses, assess fit after 30 minutes then discard lenses

Third Time-point:

3rd Pair Study Lens Assessment:	Insert 3rd pair of study lenses, assess fit after 30 minutes then discard lenses and exit

Subjects may discontinue or be discontinued from the study at any time, and the Exit Visit CRF will be completed.

8.2.2 Screening and Enrolment

The following procedures will be conducted on all subjects:

i. Allow the subject to read the Patient Information Sheet and Informed Consent Form (ICF) and explain the nature, purpose, risks of the study, etc. If they are agreeable, ask the subject to print their initials against each declaration on the last page, print their name, and then sign and date in the relevant section. The person explaining the consent and Investigator should also print their name, and then sign and date the consent form. Provide the subject with a copy of both forms, and keep the original ICF in the subject's CRF Booklet.

ii. The Investigator or a clinical assistant will review instructions and warnings for lens wear. Participants who appear unable or unwilling to follow instructions will not be enrolled onto the study.

iii. The subject is assigned with a Subject ID number according to the Enrolment Log. Subjects must be enrolled sequentially. Enter details on Enrolment Log as outlined on the form, and onto the subjects Source Document Record (see Section 13.5 for further details).

iv. Full ocular health will be established.

8.2.3 Baseline Assessment

The following baseline measurements and assessments will be recorded:

i. Subject demographics, age, sex, medications, allergies

ii. Monocular sphero-cylindrical refraction (sphere, cylinder and axis)

iii. Monocular and binocular high contrast (HC) distance visual acuity (logMAR) with best sphero-cyl spectacle refraction [D]

iv. Baseline Biometry measurements
- Corneal topography: Sim-K-readings and corneal shape factor (Medmont)
- HVID* (photo slit lamp)
- Palpebral Aperture (mm)
- Corneal sagittal height, corneal diameter (CD) (Visante OCT).

* From photographs

v. Slit lamp biomicroscopy
- Limbal Hyperaemia (0-4)
- Bulbar Hyperaemia (0-4)
- Palpebral Hyperaemia (0-4) and roughness (0-4)
- Corneal staining (0-4)
- Conjunctival fluorescein staining (0-4)
- Other findings (0-4).

See Appendix 6 for Grading Scales and measurement instructions.

Rinse away fluorescein with non-preserved saline (e.g. Sauflon saline) and allow at least 2 minutes for tear film to reform.

vi. Complete the eligibility checklist.

The subject's eligibility will be assessed for the study ensuring that the subject meets all of the inclusion/exclusion criteria, and full ocular health must be established. If the subject is eligible, then they can be fitted with the study lenses, if not eligible, then the reason should be noted on the Enrolment Log and the Exit CRF should be completed before the subject exits from the study.

Enter the subject number on to the next line of the Randomisation Log to identify the first pair of study lenses.

8.2.4 1st Pair Study Lens Assessment

i. Complete the Product Dispensing Foil Log.

ii. Record the parameters of the lenses on the 1st Pair Study Lens Assessment CRF (lens code, lens power). Lenses powers should be chosen as close as possible to the subject's spherical refraction based upon habitual contact lens information and refraction.

iii. Confirm lens is undamaged (Y/N). If yes, replace and complete Product Dispensing Foil Log.

iv. Insert 1st pair of study contact lenses.

v. Confirm subjects comfort and vision is satisfactory (Y/N). If no, then remove, replace and complete Product Dispensing Foil Log, and then repeat section v.

vi. If yes, allow approximately 30-45 minutes settling period.

vii. After settling, record the following on the 1st Pair Study Lens Assessment CRF:

Lens Fit
- Horizontal* & vertical* centration / overlap (mm)
- Post-blink movement in primary gaze (mm)*
- Version lag (mm)
- Edge tightness (0-4)
- Tightness on push-up (%)
- Diameter acceptance (mm)
- Overall fit acceptability (0-5) and reason if Grade 2 or less

* From photographs / video

viii. Remove 1st Pair Study Lenses and discard.

ix. See Appendix 6 for grading scales and measurement instructions.

8.2.5 2nd Pair Study Lens Assessment

Repeat the procedure listed in 8.2.4 using the Product Dispensing Foil Log and 2nd Pair Study Lens Assessment CRF to record the clinical test variables for the second pair of study lenses.

8.2.6 3rd Pair Study Lens Assessment

Repeat the procedure listed in 8.2.4 using the Product Dispensing Foil Log and 3rd Pair Study Lens Assessment CRF to record the clinical test variables for the third pair of study lenses.

8.2.7 Study Exit

The Study Exit Form must be completed for all subjects, who have signed the informed consent, to exit the study. This will occur either at study completion, i.e. after 3rd Study Lens Assessment, or when a subject is discontinued from the study. The exit date should also be recorded on the subjects named patient notes i.e. the Source Document Record.

Post-study follow-up visits will be scheduled if the Investigator judges this is necessary, but the Exit CRF must not be completed until any such visits have been completed.

At the study Exit Visit the following measurements are taken:

i. Monocular sphero-cylindrical refraction (sphere, cylinder and axis)

ii. Monocular distance visual acuity with sphero-cylindrical refraction (Snellen or logMAR).

iii. Slit lamp examination
- Limbal Hyperaemia (0-4)
- Bulbar Hyperaemia (0-4)
- Palpebral Hyperaemia (0-4) and Roughness (0-4)
- Corneal staining (0-4)

- Conjunctival fluorescein staining (0-4)
- Other findings (0-4).

See Appendix 5 for grading scales and measurement instructions.

Rinse away fluorescein with non-preserved saline (e.g. Sauflon saline).

iv. Post-study follow-up requirement (Y/N). If yes, the reason and date of the follow-visit must also be recorded.

If the subject is being exited due to discontinuation, further details need to be recorded on the exit form. This is described in Section 8.3 below.

8.2.8 Clinical Variables

The following table summarises the clinical measurements to be taken at each stage of the study:

Table 2: Summary of clinical assessments by visit

Procedure	Screening/ baseline	Pair 1 lens assess-ment	Pair 2 lens assess-ment	Pair 3 lens assess-ment	Exit
Subject demographics	✓				
Subject eligibility	✓				
Monocular sphero-cylindrical refraction	✓				✓
Monocular HCVA	✓				✓
Biometry- Medmont	✓				
Biometry- Visante OCT	✓				
Slit lamp biomicroscopy	✓				✓
Lens fit and comfort assessment		✓	✓	✓	

8.3 Subject Discontinuation

Subjects may be discontinued from the study at the discretion of the Investigator or the subject.

In the event of discontinuation, the Study Exit Form must be completed and the study exit date recorded on the Source Document Record. The Investigator will indicate the primary reason for discontinuation by ticking one of the boxes provided on the bottom half of the Exit Form. Further details can be provided in the 'comments' section if necessary.

8.4 Post-Study Follow-up

A post-study follow-up visit must be scheduled if the subject exhibits any slit lamp findings which are clinically different from baseline upon discontinuation or completion of the study, unless the Investigator judges that no follow-up is warranted.

Post-study follow-up visits will be recorded on the Unscheduled Visit CRF. All variables listed on the forms must be completed unless the subject exhibits a condition that prohibits their completion. If this is the case, a written explanation is required in the comments section.

The study Exit form should not be completed until all post study follow-up visits have been completed.

9 ADVERSE EVENTS

An Adverse Event (AE) is defined as any unfavourable or unintended sign (including an abnormal finding), symptom or disease temporarily associated with the use of a study device whether or not related to the study device. All AEs, both ocular and non-ocular (but related to the test or control lens or to the study procedures), will be monitored.

The Investigator will be required to judge whether or not an AE is device-related. In the case where more than one diagnostic finding is associated with an AE, the event will be counted as one event and categorized under the most significant of the findings.

The Investigator will be required to report all device-related AEs to the REC. The seriousness of an AE is categorized as being either serious, significant, or non-significant:

- Serious – Any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

- Significant – Symptomatic and warrant discontinuation of contact lens wear (temporary or permanent).

- Non-Significant – Usually asymptomatic and do not warrant discontinuation of contact lens wear (temporary or permanent). However, as a precautionary measure, the Investigator may decide to take action.

For additional information, questions, or assistance in recording potential AEs, the Investigator should refer to VCR Standard Operating Procedure for Good Clinical Practice (SOP-GCP-161).

9.1 Adverse Event Categorisation

The Investigator will be required to rate the likelihood of an event being lens-related (Possible, Probable, Highly Probable) or non-lens-related (No, Doubtful) in their adverse event evaluation.

9.2 Adverse Event Reporting

Upon discovery of an AE, the Investigator will complete an Adverse Event Form (AE form) to capture the event.

If applicable, the Investigator will notify the REC as per the REC requirements.

9.3 Device-Related Adverse Event Documentation

Investigators are required to document and follow-up all adverse events.

All adverse events are documented on an AE Form (Appendix 1) upon event discovery. For all ocular AEs, one AE form is used per eye. For AEs which are non-ocular but related to the study device (test or control) or to the study procedures, only one AE Form needs to be completed per AE.

Procedure:

The Investigator has the responsibility to:

1. Complete as much information as possible on the AE Form upon event discovery. This includes:
    - A detailed description of the adverse event and a diagnosis, including a probable cause.
    - Detailed drawings that detail size, location and depth, or photographs (if necessary).
    - Likelihood of the adverse event being device-related.
2. If appropriate, report the AE to the Research Ethics Committee within the specified timelines (see Reporting of Adverse Events section 9.2).
3. Follow study subject until resolution recording all information on an unscheduled visit CRF, including VA, symptoms and slit lamp findings, resolution and permanent sequelae if any.
4. Complete all remaining information as required on the AE Form. If follow-up of the adverse event is required, the resolution of the AE can only be completed when all follow-up visits are done. The following additional information will also be completed on the AE resolution form:

- Outcome, ocular sequelae if any
- Whether the patient is discontinued from the study as a result of the AE

9.4 Adverse Event Follow-up

The Investigator will conduct follow-up examinations until the condition has either: returned to pre-event status, stabilized, or been satisfactorily explained.

If the subject is referred for medical attention, they will be tracked by the Investigator until the aforementioned conditions are met.

Follow-up data will be collected on Unscheduled Visit CRFs and on the AE Form.

9.5 Study Completion

The study is completed when all subjects have completed the third pair study lens assessment or have been discontinued.

10 DATA MANAGEMENT

10.1 Data Quality Assurance

Before the final closing of the database, the data will be checked and any subsequent omissions and discrepancies resolved before analysis as per VCR SOPs.

10.2 Data Entry and Storage

Data shall be completed on the CRFs and hand entered into a database using DACs software and then exported to an Excel database (Microsoft). The statistical analyses will be completed using SAS software.

11 SAMPLE SIZE AND STATISTICAL METHODS

11.1 Sample Size Rationale

A sample size of 60 subjects showing a 90% success rate would give an 80% confidence interval of ± 5.0%. This would statistically differentiate success rates of 85% and 95%.

A sample size of 60 is sufficient to detect a mean difference of 5 (0-100) in tightness, or 0.2 mm in corneal overlap assuming the standard deviation of the mean differences in Table 2 below and assuming α=0.05 with a power of 95%.

Table 2: Sample Size Justification:

	Sample Size	
	Tightness (0-100)	**Corneal overlap (mm)**
Mean of paired difference	5	0.2
SD of paired difference	10	0.4
Minimum sample size per group	42	42

11.2 Level of Statistical Significance

The overall type I error rate will be preserved at 5%. To preserve type I error control, the study hypotheses will be evaluated using a sequential gate-keeping strategy. All tests will be two-sided. The three co-primary hypotheses will be simultaneously evaluated using α=0.05, all of which must be met in order to satisfy the primary objective of this study.

11.3 Analysis Population

The primary hypotheses will be analysed on all randomized subjects who have successfully completed the study without a protocol deviation that is deemed to impact the assessment of the primary hypotheses (i.e. the per-protocol population).

11.4 Summary Tables

Summary tables (descriptive statistics and/or frequency tables) will be provided for all variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

11.5 Statistical Analysis

11.5.1 Success Rates – Two Designs versus One Design

Fit acceptance (0=Unacceptable, 1=Acceptable) will be analysed using a generalized linear mixed model with a binary distribution and a logit link function. Lens type will be included as a fixed effect and subject will be included as a random effect.

If the incidence rate is too low or there are problems with the convergence of the above model, the method of Wilson[5] will be used to evaluate the confidence intervals.

11.5.2 Success Rates – Actual versus Theoretical

Fit acceptance (0=Unacceptable, 1=Acceptable) will be analysed using a generalized linear mixed model with a binary distribution and a logit link function. Lens type, period, and the lens by period interaction will be included as fixed effects and subject will be included as a random effect. The proportion of eyes with acceptable lens fit with each lens type will be calculated with 95% confidence intervals. These confidence intervals will be compared to the theoretical success rates.

If the incidence rate is too low or there are problems with the convergence of the above model, the method of Wilson[5] will be used to evaluate the confidence intervals.

11.5.3 Fitting Characteristics – Actual versus Theoretical

The fitting characteristics will be analysed separately for tightness and corneal overlap using linear mixed models. The regression models will include the experimental design factors: lens type, period, and the lens by period interaction as fixed effects, and subject as a random effect. Comparisons will be carried out using 95% confidence intervals constructed of least-square means (LSM) from the linear mixed models.

11.5.4 Supplementary Analysis

Appropriate additional *post hoc* analyses may be undertaken.

11.6 Interim Analysis

There will be no interim analyses and, therefore, there are no criteria for early termination of the study on statistical grounds.

12 POTENTIAL RISKS AND 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 new contact lens products.

This study is considered to be a non-significant risk study based on International Standards Organization (ISO) guidelines due to the relatively short duration of wear (30mins) of a marketed lens in the study.

The risks to participants in this study are similar to those associated with normal daily wear of soft contact lenses.

13 GENERAL STUDY MANAGEMENT

13.1 Relevant Standards

This protocol has been developed in accordance with the following:

- ISO 14155-1:2011 Clinical Investigation of Medical Devices for Human Subjects
- ISO 11980:2012 contact lenses and contact lens care products – Guidance for clinical investigations.
- ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP)
- Declaration of Helsinki

The study will also be carried out in accordance with the Visioncare Research Quality Management System (ISO 9001:2008).

13.2 Ethics Review

The study Protocol, Informed Consent Form and Participant Information Sheet will be submitted to the Research Ethics Committee - National Research Ethics Service (NRES) and to Aston University REC. A favourable opinion will be received prior to undertaking the study. The approval letter should clearly mention the approval/favourable opinion of the Protocol, Informed Consent Form and Participant Information Guide, including respective version dates.

If significant protocol changes which require the preparation of an amendment are necessary, written approval will be obtained prior to implementation.

13.3 Protocol Deviations

The Investigators will not deviate from the protocol without written approval from NRES and Aston University REC and will require a protocol amendment. However, in medical emergencies, the Investigator will use their judgement and remove the subject from immediate hazard.

If an unexpected deviation from the protocol occurs, the Investigator will document their findings until resolution on a follow-up assessment form.

13.4 Premature Termination of the Study

The Investigator reserves the right to terminate the study at any time for any reason, including adverse effects. If it is determined that an unanticipated adverse device effect presents an unreasonable risk, then the entire investigation or part of the investigation presenting the risk shall be terminated as soon as possible. A written statement fully documenting the reasons for such termination will be provided to NRES.

13.5 Source Documentation

Unless otherwise documented, the CRFs will be considered the source document and will be completed to comply with GCP guidelines. A permanent record will be made within the patient's notes to document the subject's involvement in a clinical research study and will include:

- Study number and Subject ID
- Confirmation that subject met eligibility criteria
- Confirmation that subject signed the informed consent

- Confirmation that subject received a signed and dated copy of informed consent
- Date enrolled
- General notes
- Reportable protocol deviations
- Adverse events
- Exit date
- Whether subject completed the study or discontinued
- Investigator's signature

13.6 Monitoring

Since this is an investigator initiated study, there will be no external monitoring, although all activities will comply with ISO14155 and ISO 11980.

13.7 Audits

The Investigator shall permit the NRES to inspect its facilities, equipment, and study-related records, data and other documents upon reasonable notice. In addition, the NRES may conduct such inspections as they deem necessary at any time whether or not advanced notice is given by them. If such notice is in writing, a copy with any attachments thereto shall be added to the study documents.

13.8 Records Retention

The study lens material is already on the market; therefore, the study documents should be kept for a minimum of two years after the end of the study according to the ICH GCP guidelines.

13.9 Confidentiality and Publication

By signing the Informed Consent Form, the subject authorises the Investigator to access their optometric clinical records. The authorisation will be indefinite; however, subjects will have the right to reverse this authorisation at any time.

Any electronic records will also be handled in accordance with the UK Data Protection Act (1998).

14 REFERENCES

1. Hall L, Hunt C, Young G, Wolffsohn J. Factors affecting corneoscleral topography. *Invest Ophthal Vis Opt* 2013; 54:3691-3701.

2. Young G. Mathematical model for evaluating soft contact lens fit. *Optom Vis Sci* 2014; 91:167-76.

3. Young G, Hall L, Sulley A, Osborn-Lorenz K, Wolffsohn J. The inter-relationship of soft contact lens diameter, base curve radius and fit. *Optom Vis Sci* 2017; 94:458-65.

4. Sulley A, Young G, Hunt C. Retention rates in new contact lens wearers. *Eye Cont Lens* 2017 In press.

5. Wilson, E. B. Probable inference, the law of succession, and statistical inference, *J Am Stat Assoc*, 1927; 22:209-12.

APPENDIX 1

Template Adverse Event Form

ADVERSE EVENT FORM

(Immediate Notification)

Please notify Visioncare Research of this event IMMEDIATELY in the following way:

complete and fax page 1 or telephone to relay the information
Tel: 01252 718719 Fax: 01252 718720
If required, Visioncare Research will advise how to notify the appropriate research ethics committee.

Subject ID: ___ / ____ / _____ Date of visit when event discovered: ___ / __ / ___

Visit when event discovered: ☐ 1st assessment ☐ 2nd assessment ☐ 3rdassessment ☐ Exit

General Information

Data entered by eye (only one eye per form)

Eye: (tick one box only) ☐ Right ☐ Left

Lens code: .....

Wearing schedule at time of AE: ☐ Daily Wear

Spectacle refraction: _____ / _____ x _____

Best corrected distance VA: .....

Date event began: ____ / ___ / ___

Date subject entered the study: ____ / ___ / ___

Diagnosis

see Adverse Event section in protocol

Symptoms and history: .....

Significant slit lamp findings re[illegible] t[illegible] Au .....

Diagnosis: .....

Event seriousness: (tick one box only) ☐ Serious ☐ Significant ☐ Non-significant

Do you consider the event device related: ☐ Highly Probably ☐ Probable ☐ Possible ☐ No

Event severity: (tick one box only) ☐ Mild ☐ Moderate ☐ Severe

Is corneal infection suspected? ☐ Yes ☐ No

Possible cause: (If not known tick box) ☐ .....

Page 2 (of 2)
(Action, Follow-up & Resolution)

Study No: TRTN-501
ADVERSE EVENT FORM

Subject ID: __ / ____ / ____ Eye: R / L Date discovered: ___/___/ ___

Treatment / Action

Medication prescribed: .....

.....

.....

.....

.....

Initial treatment (including referral if required): .....

.....

.....

.....

.....

Follow-up

If no follow-up required tick box: ☐

otherwise provide follow-up dates below, and at each visit record details on an Unscheduled Visit Form

Follow-up dates: ___ / __ /___ ___ / __ /___ ___ / __ / ___

AE resolved at this visit? AE resolved at this visit? AE resolved at this visit?
[ ] Yes ☐ No ☐ Yes ☐ No [ ] Yes ☐ No

Outcome

Only complete this section when event has resolved

Total number of days out of lens e_____ da_

Spectacle refraction and best corrected distance VA (at resolution): _____ / _____ x _____ _____

Permanent sequelae to eye following event? ☐ Yes ☐ No

If Yes describe: .....

.....

.....

Discontinued from study due to event? ☐ Yes ☐ No

If Yes, date of discontinuation: ___ / __ / 2014

APPENDIX 2

Template Sample Enrolment and Randomisation Logs

TRTN-501

SAMPLE ENROLMENT LOG

A maximum of 20 subjects may be enrolled. All subjects must be enrolled sequentially.

Subject ID Site /Sub/Initials	**Subject Name**	**Enrolment Date** **(Consent signed)** (dd/mm/yy)	**Subject Eligible**	**Large HVID / CD**	**Reason if not eligible**
*01 / 01 / **JS***	***John SMITH***	***10 / 01 / 14***	***Y***	***Y***	
01 / 01 /		/ /	Y / N	Y / N	
01 / 02 /		/ /	Y / N	Y / N	
01 / 03 /		/ /	Y / N	Y / N	
01 / 04 /		/ /	Y / N	Y / N	
01 / 05 /		/ /	Y / N	Y / N	
01 / 06 /		/ /	Y / N	Y / N	
01 / 07 /		/ /	Y / N	Y / N	
01 / 08 /		/ /	Y / N	Y / N	
01 / 09 /		/ /	Y / N	Y / N	
01 / 10 /		/ /	Y / N	Y / N	
01 / 11 /		/ /	Y / N	Y / N	
01 / 12 /		/ /	Y / N	Y / N	
01 / 13 /		/ /	Y / N	Y / N	
01 / 14 /		/ /	Y / N	Y / N	
01 / 15 /		/ /	Y / N	Y / N	
01 / 16 /		/ /	Y / N	Y / N	
01 / 17 /		/ /	Y / N	Y / N	
01 / 18 /		/ /	Y / N	Y / N	
01 / 19 /		/ /	Y / N	Y / N	
01 / 20 /		/ /	Y / N	Y / N	

TRTN-501

SAMPLE RANDOMISATION LOG

Subjects should only be entered onto the Randomisation Log once they have been found to be eligible for the study.

Subject ID Site /Sub/Initials	**Randomisation Date** (dd/mm/yy)	**Pair 1**	**Pair 2**	**Pair 3**
*01 / 01 / **JS***	***10/08/17***	***A***	***B***	***C***
01 / 01 /		*A*	C	*B*
01 / 02 /		*B*	*A*	*C*
01 / 03 /		*A*	*C*	*B*
01 / 04 /		*B*	*C*	*A*
01 / 05 /		*A*	*B*	*C*
01 / 06 /		*C*	*B*	*A*
01 / 07 /		*C*	*B*	*A*
01 / 08 /		*A*	*C*	*B*
01 / 09 /		*B*	*C*	*A*
01 / 10 /		*B*	*A*	*C*
01 / 11 /		*A*	*C*	*B*
01 / 12 /		*C*	*B*	*A*
01 / 13 /		*A*	*B*	*C*
01 / 14 /		*B*	*A*	*C*
01 / 15 /		*C*	*A*	*B*
01 / 16 /		*B*	*C*	*A*
01 / 17 /		*A*	*B*	*C*
01 / 18 /		*C*	*A*	*B*
01 / 19 /		*B*	*C*	*A*
01 / 20 /		*A*	*B*	*C*

APPENDIX 3

Template Product Accountability Log

(1 Page sample only)

TRTN-501
PRODUCT ACCOUNTABILITY LOG

SITE NUMBER ____

1. When product is received, record power (if applicable), base curve (if applicable), expiry date (if applicable), lot numbers, date of receipt and number received.
2. Tally (tick mark) under "No. Dispensed" column when product is dispensed or given to a subject.
3. Insert the number of unused product, this should equal the “No. Received” minus “No. Dispensed”.
4. Please sign, date and return this sheet with the product when all subjects have been exited.

Power	Base Curve	Expiry Date	Lot #	Date Rec’d at Site	No. Rec’d	No. Dispensed	No. Returned to Site	No. unused to be returned	OFFICE USE ONLY No. Destroyed
TOTALS									

Investigator’s signature: _____ Date: _____/_____/_____

APPENDIX 4

Template Product Dispensing Foil Log

(1 Page sample only)

TRTN-501
PRODUCT DISPENSING FOIL LOG

Date/Page: _____/__ Investigator's Initials: _____ Subject ID: __ / ____ / ____

Please affix the OD and OS foil from the dispensed study lenses to the table below and record the applicable information. After each lens foil is affixed to the page the site staff member dispensing the lenses should initial and date the entry in the space provided in the middle column.

OD Foil	Visit Information	OS Foil
	Lens Code _____ **Are Additional lenses Needed: □ Yes □ No** **If yes please affix foils below.**	
OD Foil	**Visit Information**	**OS Foil**
	Lens Code _____ **Are Additional lenses Needed: □ Yes □ No** **If yes please affix foils below**	
OD Foil	**Visit Information**	**OS Foil**
	Lens Code _____ **Are Additional lenses Needed: □ Yes □ No** **If yes please affix foils below.**	
OD Foil	**Visit Information**	**OS Foil**
	Lens Code _____ **Are Additional lenses Needed: □ Yes □ No** **If yes please continue on next page of log.**	

APPENDIX 5

Grading Scales & Measurement Instructions

GRADING & MEASUREMENT SYSTEM (TRTN-501)

VARIABLE	ASSESSMENT METHOD	GRADING/MEASUREMENT SYSTEM
Vision		
Distance VA – High contrast	Assessed using computer generated logMAR chart.	logMAR visual acuity (VA) to nearest letter.
Biometry		
Corneal Topography Sim-K	Assessed using Medmont Corneal Topographer.	To nearest 0.01 mm
Corneal Topography Corneal Shape Factor (P-value)	Assessed using Medmont Corneal Topographer.	To nearest 0.01 mm
Iris Diameter	Assessed using photographs from photo slit lamp (10x or 30x magnification), at primary gaze and using the eyepiece graticule.	To nearest 0.1 mm
Palpebral Aperture	Assessed using slit lamp in 10x or 30x magnification, at primary gaze and using the eyepiece graticule.	To nearest 0.1 mm
Corneal Sagittal Height	Assessed using Visante OCT.	To nearest 0.01 mm
Corneal Diameter	Assessed using Visante OCT.	To nearest 0.01 mm
Lens Fit **- assessed using photo / video slit lamp (10x or 30x magnification)**		
Horizontal and Vertical Centration / overlap	Assessed using photographs / video, primary gaze and eyepiece graticule. Lens centration will be recorded by degree and direction in the primary position.	To nearest 0.1mm For Superior or Nasal record +ve value For Inferior or Temporal record -ve value
Post-Blink Movement in Primary Gaze	Assessed using photographs / video, primary gaze and using the eyepiece graticule immediately after the blink - lower lid to be depressed only if necessary for observation.	To nearest 0.1mm
Version Lag	Assessed on D / L gaze.	To nearest 0.1mm

VARIABLE	ASSESSMENT METHOD	GRADING/MEASUREMENT SYSTEM
Edge Tightness	Assessed using primary gaze and eyepiece graticule.	Grade 0-4 where: 0 Gross edge stand-off/fluting 1 Loose, occasional edge lifting 2 Optimum 3 Tight, mild vessel compression 4 Conjunctival indentation and/or compression against immobile lens
Tightness / Push-up	Assessed by digital push-up test (gentle push of the lens upward using the lower lid) with eye in primary gaze position and observing ease of push-up and speed of return to original position.	Grade 0%-100% continuous scale where: 100% No movement 50% Optimum 0% Falls from cornea without lid support
Diameter Acceptance	Assessed using primary gaze and the eyepiece graticule.	To nearest 0.1mm
Overall Fit Acceptance	Assessed by the Investigator based on lens fit alone (i.e. not comfort or vision).	Grade 0-5 & add reason if Grade 2 or less: 0 Should not be worn 1 Should not be dispensed although no immediate danger 2 Borderline but unacceptable 3 Min. acceptable, early review 4 Not perfect but OK to dispense 5 Perfect
Comfort		
Subjective Comfort	Ask the subject the following: "Using a 0-10 scale, please rate the lens comfort as it is now (10=Can't feel the lenses, 0=painful)."	0-10 scale
Biomicroscopy		
Limbal Hyperaemia	Assessed using white light and low-medium magnification.	Grade 0-4: 0 NONE: No hyperaemia 1 TRACE: Slight limbal hyperaemia (mild segmented) 2 MILD: Mild limbal hyperaemia (mild circumcorneal) 3 MODERATE: Significant limbal hyperaemia (marked segmented) 4 SEVERE: Severe limbal hyperaemia (marked circumcorneal)

VARIABLE	ASSESSMENT METHOD	GRADING/MEASUREMENT SYSTEM
Bulbar Hyperaemia	Assessed using white light and low-medium magnification.	Grade 0-4: 0 NONE: No hyperaemia 1 TRACE: Slight regional hyperaemia 2 MILD: Diffuse hyperaemia 3 MODERATE: Marked regional or diffuse hyperaemia 4 SEVERE: Diffuse episcleral or scleral hyperaemia
Palpebral Roughness	Assessed using white light, low-medium magnification and CCLRU images for reference.	Grade 0-4: 0 Uniform satin appearance off conjunctiva 1 Trace, slight loss of smoothness 2 Mild, or scattered papillae/ follicles, less than 1mm in diameter. 3 Moderate, significant papillae / follicles, less than 1mm in diameter. 4 Severe, localised or generalised papillae / follicles 1mm or more in diameter
Corneal Staining Grade	Assessed using fluorescein, blue light, yellow filter and full beam with medium magnification.	0 NONE: No staining 1 TRACE: Minimal superficial diffuse staining or stippling, or trace abrasion or foreign body tracks 2 MILD: Regional or diffuse punctate staining, or mild abrasion or foreign body tracks 3 MODERATE: Significant dense coalesced staining, corneal abrasion or foreign body tracks 4 SEVERE: Confluent abrasions greater than 2mm diameter, ulcerations, epithelial loss, or full thickness abrasion
Conjunctival Staining	Assessed using fluorescein, blue light, yellow filter and full beam with low-medium magnification. Ignore conjunctival indentation with no staining.	0 None 1 Minimal diffuse punctate 2 Coalescent punctate 3 Confluent 4 Widespread confluent
Other Significant Findings	Describe finding and grade severity	0 None 1 Trace 2 Mild 3 Moderate 4 Severe

MEASUREMENT INSTRUCTIONS

CORNEAL STAINING

Materials Needed: Soduim fluorescein impregnated strips and Yellow filter.

The type (severity) of corneal staining will be evaluated with the slit-lamp using blue light and a yellow filter (e.g. #12 Wratten). Both eyes will be evaluated. The fluorescein used throughout the study will be standard fluorescein sodium ophthalmic strips (e.g. Chauvin Fluorets).

i. Wet a fluorescein strip using non-preserved sterile saline.

ii. Instil one drop of fluorescein onto either: a) the upper bulbar conjunctiva of the right eye with the upper lid retracted and the patient looking downwards; or b) the lower lid margin with the patient looking upwards.

iii. Instruct the subject to blink a few times, and **wait 1-2 minutes** before examining the eye. Note that excess fluorescein in the tear film can mask corneal staining.

iv. Examine for staining through a biomicroscope, using blue light and a yellow filter. The magnification should be medium and the illumination high.

v. Grade and record the type of corneal staining using the scales below.

vi. N.B. Do not record staining secondary to debris, dimple veiling, or pooling. If a region has more than one type (severity) of staining, grade and record the most severe staining.

vii. Repeat the assessment for the left eye.

Grade of Corneal Staining (Severity):

0 NONE: No staining.
1 TRACE: Minimal superficial diffuse staining or stippling, or trace abrasion or foreign body tracks.
2 MILD: Regional or diffuse punctate staining, or mild abrasion or foreign body tracks.
3 MODERATE: Significant dense coalesced staining, corneal abrasion or foreign body tracks.
4 SEVERE: Confluent abrasions greater than 2mm diameter, ulcerations, epithelial loss, or full thickness abrasion.