NCT03208673

Study ID: CMO-EAME-EYE-0485

Title: Optive Brand For Day And Night Dry Eye Management

Protocol Date: 18 May 2017

OCULAR TECHNOLOGY GROUP - *International*

ALLERGAN – CONFIDENTIAL

OPTIVE BRAND FOR DAY AND NIGHT DRY EYE MANAGEMENT

CLINICAL INVESTIGATIONAL PLAN

Sponsor: Allergan Pharmaceuticals International Ltd

OTG-*i* Study Number and Version: ID17-04 Version 1.0

Study Sponsor Number: CMO-EAME-EYE-0485

Issue Date: 18-May-2017

SAFETY REPORTING DETAILS:

SAE REPORTING FAX NUMBER:

BACK UP FAX NUMBER:

E-mail:

AUTHOR

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Clinical Investigational Plan

OPTIVE BRAND FOR DAY AND NIGHT DRY EYE MANAGEMENT

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Protocol Signature Page

As Principal Investigator, I agree to conduct this study in accordance with all applicable laws and regulations and in compliance with the provisions of this Clinical Investigational Plan.

I am responsible for ensuring that the investigation is conducted according to this plan and for protecting the rights, safety, and welfare of the research participants.

_____	_____	_____
Principal Investigator Name (printed)	Signature	Date

Confidentiality Statement

The information in the following document is provided to you as an investigator, potential investigator, or consultant, for review by you, your staff, and applicable Ethics Committee or Institutional Review Board, and is considered confidential. It is understood that the information will not be disclosed to others without written authorization from OCULAR TECHNOLOGY GROUP - *International*, except to the extent necessary to obtain informed consent from the study participants.

Each party shall keep confidential all information which is received from the other party and which is specified by the disclosing party to be confidential at the time of disclosure, and direct its employees, agents and sub-contractors to do the same. This obligation shall not apply to information which (i) either at the time of disclosure or after disclosure is published or generally available to the public other than through a breach (ii) is already in the receiving party's possession at the time of receipt and which was not acquired directly or indirectly from the disclosing party (iii) is acquired by the receiving party in good faith from a third party (iv) is required to be disclosed by law or (v) has been authorised to be disclosed in writing, by the disclosing party

DOCUMENT CHANGE HISTORY

Revision	Originator	Description of Change(s)	Date
1.0	[redacted]	Original document	18th May 2017
1.1			
1.2			
1.3			

Table of Contents

1 Overall Synopsis

Study Sponsor	Allergan Pharmaceuticals International Ltd. Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland.
Title of Study	Optive Brand For Day And Night Dry Eye Management
Protocol Number	CMO-EAME-EYE-0485
Phase or type of study	The study will be an open label, bilateral, prospective, interventional post marketing, clinical study.
Investigator(s) / Site(s)	OCULAR TECHNOLOGY GROUP - International (OTG-i), 66 Buckingham Gate, London, SW1E 6AU UK.
Planned Duration of Study	6 months
Study Population	Up to 40 participants to have 35 participants enrolled into the investigational phase at the end of Visit 2 to achieve a cohort of 30 participants completing the study.
Inclusion Criteria	The inclusion criteria will include the following: • Age at least 18 years; • OSDI score of ≥ 23; • Ocular comfort at waking <65 on 100-point scale; • Conjunctival staining Grade ≥ 2 (scale 0 to 4) in at least one eye; • Use of eyedrops for the relief of dry eye symptoms for at least one month.
Exclusion Criteria	The exclusion criteria will include the following: • Use of Benzalkonium Chloride (BAK) preserved eyedrops in the last month; • Use of Optive brand eyedrops in the last month; • Contact lens wear during the study; • Known pregnancy or lactation during the study period; • Enrolment of investigator's office staff, relatives, or members of their respective households; • Participation in any clinical trial within 30 days of the enrolment visit.
Planned Start Date	July 2017

Objective(s)	The primary objectives of the study will be to: i. Quantify the effect of a one-month treatment involving an eyedrop / gel combination on overall dry eye symptomatology on moderate to severe dry eye sufferers; ii. Evaluate the effect of a one-month treatment involving an eyedrop / gel combination on conjunctival staining moderate to severe dry eye sufferers. The secondary objective of the study will be to quantify the effect of a one-month treatment involving an eyedrop / gel combination on symptomatology upon waking on moderate to severe dry eye sufferers. [redacted]
Hypotheses	The primary hypotheses that will be tested will be that: i. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will reduce overall dry eye symptomatology; ii. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will decrease conjunctival staining. The secondary hypotheses that will be tested will be that a one-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will reduce symptomatology upon waking. [redacted]
Efficacy Endpoint(s)	The primary end points will be: i. OSDI total score; ii. Measured lissamine green bulbar conjunctival staining (mm^2). The secondary end points will be symptomatology upon waking (VAS scale). [redacted]

<table>
<tr><td>Efficacy Procedure(s)</td><td colspan="2">The primary response procedures will be:
i. OSDI questionnaire;
ii. Digital photography of lissamine green staining of the exposed bulbar conjunctiva.
The secondary response procedures will be:
i. VAS comfort & symptomatology questionnaire;
[redacted]</td></tr>
<tr><td>Safety Procedure(s)</td><td colspan="2">The safety procedures will be biomicroscopy, identification of adverse events, measurement of Snellen Visual Acuity and identification of prevalence of adverse events.</td></tr>
<tr><td>Population Profiling Procedure(s)</td><td colspan="2">The procedures to profile the population key characteristics will be:
i. Demographics and ocular history questionnaire (including concomitant treatment);
ii. OSDI questionnaire;</td></tr>
<tr><td rowspan="2">Experimental Design</td><td>☐ Retrospective
X Prospective</td><td>X Non-Randomized
☐ Randomized</td></tr>
<tr><td>☐ Single masked (participant)
☐ Single masked (investigator)
☐ Double masked
☐ Sponsor masked
X Open label</td><td>X Single group
☐ Parallel group
☐ Crossover
☐ Contralateral</td></tr>
</table>

Run-in Product(s)	REFRESH® Contacts® Unitdose, a CE marked eye lubricant eyedrop, manufactured by Allergan Pharmaceuticals Ireland, containing 0.5% carboxymethylcellulose sodium.	
Test Product(s)	The treatment regimen to be tested will be: i. Optive® Fusion™ a CE marked eyedrop, manufactured by Allergan Pharmaceuticals Ireland, containing 0.1% sodium hyaluronate, 0.5% carmellose sodium and 0.9% glycerol for daytime use. The eyedrop will be used as needed up to four times a day but at least twice a day. ii. Optive® Gel Drop a CE marked gel manufactured Allergan Pharmaceuticals Ireland, containing 0.5% carboxymethylcellulose sodium and 0.9% glycerol for night time use. The eyedrop will be used once in the evening; the gel drop being instilled any time during the last hour prior to sleep	
Study Visits	Three scheduled visits over a five-week period. i. Enrolment visit; ii. Baseline / Dispensing visit (7 ± 1 days from enrolment); ii. One month follow-up visit (30 ± 3 days from dispensing.	
Keywords	Optive Fusion, Optive Gel Drops, Refresh Contacts Unitdose, OSDI, Conjunctival Staining, Tear Film Kinetics, Dry Eyes	
Regulatory Status	This trial requires Ethics Committee (EC) approval prior to initiation.	
Responsibilities	Sponsor	Name: Allergan Pharmaceuticals International Ltd.
	CRO and Data Management	OCULAR TECHNOLOGY GROUP - International
	Legal Representative (where applicable)	

2 Introduction and Rationale

2.1 *Background*

Tear film physiology differs greatly between the waking and sleeping periods. During the waking period the tear film is an aqueous based film produced by the lacrimal gland and connected to the ocular surface via the inner mucin layer, and protected from evaporation by the outer lipid layer. Aqueous, which accounts for 98% of the overall tear film, is distributed onto the ocular surface and a proportion of the aqueous is eliminated with each blink. In contrast, during sleep aqueous production stops and the tear film becomes a gel like structure dominated by mucin and lipids [1].

Anomalies of any of the layers of the tear film lead to dry eye complaints which vary greatly not only in their level of severity but also in their diurnal characteristics. Typically, dry eye complaints are least during the day and most marked either in the evening or upon waking, suggesting different potential mechanisms [2].

The physiological characteristics of the tear film would suggest that a different dry eye treatment should be implemented for the waking and sleeping phases of the day: aqueous supplementation and surface protection from the atmosphere during waking hours and gel supplementation during sleep; the latter being particularly important for those sufferers with highest level of complaints upon waking.

In addition to symptomatology, dry eyes are characterised by changes in the tear film and / or the ocular surface depending upon the patients. Reported tear film anomalies include destabilisation (shorter tear film break up time), poorer ocular surface coverage (decreased tear film kinetics) and increased tear film evaporation. The ocular surface modifications are corneal fluorescein staining and conjunctival (exposed bulbar and palpebral) lissamine green staining, the latter being the most prevalent. Another ocular tissue change reported is increased redness due to the inflammatory process associated with dry eye [3].

2.2 *Objectives*

The primary objectives of the study will be to:

i. Quantify the effect of a one-month treatment involving an eyedrop / gel combination on overall dry eye symptomatology on moderate to severe dry eye sufferers;
ii. Evaluate the effect of a one-month treatment involving an eyedrop / gel combination on conjunctival staining on moderate to severe dry eye sufferers.

The secondary objective of the study will be to:

Quantify the effect of a one-month treatment involving an eyedrop / gel combination on symptomatology upon waking on moderate to severe dry eye sufferers.

2.3 *Hypothesis*

The primary hypotheses that will be tested will be that:

i. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will reduce overall dry eye symptomatology;
ii. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will decrease conjunctival staining.

The secondary hypothesis that will be tested will be that:

One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will reduce symptomatology upon waking.

[redacted]

2.4 *Endpoints*

The primary end points will be:
i. OSDI total score.
ii. Measured lissamine green bulbar conjunctival staining (mm^2).

The secondary end points will be symptomatology upon waking (VAS scale).

[redacted]

3 Study Sponsor and Investigators

3.1 *Study Sponsor*

The Sponsor for this investigation will be Allergan Pharmaceuticals International Ltd. Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland.

3.2 Clinical Research Organization

The investigation will be carried out by OCULAR TECHNOLOGY GROUP - International (OTG-i), Lower Ground Floor, 66 Buckingham Gate, London SW1E 6AU (Study Director [redacted]

3.3 *Study Site(s)*

The study site will be OCULAR TECHNOLOGY GROUP - International (OTG-i), Lower Ground Floor, 66 Buckingham Gate, London SW1E 6AU

3.4 *Clinical Investigators*

The study Chief Investigator will be

3.5 *Medical Monitor*

The medical monitor at the OTG-i Research Clinic will be ; the medical monitor is contracted to OTG-i Research Clinic for this activity

3.6 *Data Controller*

The statistical analysis and data management control will be conducted by OCULAR TECHNOLOGY GROUP – International. The data controller will be

3.7 *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 participants with a copy of the consent form written in a language the participant understands; in this study all documentation will be in English and only participants fluent in English will take part. 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. Participants also will be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must 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 proportionate review). The investigation will not start until approval has been received by the site.

4 Test Materials

4.1 *Test Products*

The treatment regimen will be:

i. Optive® Fusion a CE marked eyedrop, manufactured by Allergan Pharmaceuticals Ireland, containing 0.1% sodium hyaluronate, 0.5% carmellose sodium and 0.9% glycerol for daytime use. The eyedrop will be used as needed up to four times a day but at least twice a day;

ii. Optive® Gel Drop a CE marked gel manufactured by Allergan Pharmaceuticals Ireland, containing 0.5% carboxymethylcellulose sodium and 0.9% glycerol for night time use. The eyedrop will be used once in the evening; the gel drop being instilled any time during the last hour prior to sleep.

The treatment regimen will be used for one month (30 ± 3 days).

4.2 *Run-in Product*

The run-in product will be REFRESH® Contacts® Unitdose, a CE marked eye lubricant eyedrop, manufactured by Allergan Pharmaceuticals Ireland, containing 0.5% carboxymethylcellulose sodium. The eye drop will be used as needed up to four times a day but at least twice a day for one week (7 ± 1 days)

4.3 *Adjunct Products*

No other system will be used and the products will be used according to their indication and discarded at the completion of the period of use.

5 Test Population

5.1 *Recruitment Procedure*

The prospective participants will be selected from the existing clinical population of the OTG-i Research Clinic or recruited my means of an advertisement if necessary. The participants fulfilling the criteria for inclusion and none of the exclusion criteria will be invited in a random fashion to participate in the study until the test population is achieved.

The prospective participants will initially be contacted by telephone, the investigation will be explained in detail and if interested an enrolment / test visit will be scheduled. The prospective participants will be sent a copy of the Participant Information Sheet and Informed Consent by email prior to the visit, upon arrival at the clinic the participants will be given a printed copy of the consent form and the study will be explained to them. The participants will be asked to read and sign the Informed Consent prior to any evaluation.

5.2 *Number of Participants*

Up to 40 participants will be screened for 35 participants to be enrolled into the investigational phase at the end of Visit 2 with a view to achieve a cohort of 30 participants completing the study as per the protocol.

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 18 years old;
ii. Moderate to severe dry eye symptomatology based up an OSDI score of ≥ 23;
iii. Ocular comfort at waking <65 on 100-point scale;
iv. Conjunctival staining Grade ≥ 2 (scale 0 to 4) in at least one eye;
v. Use of eyedrops for the relief of dry eye symptoms for at least one month.
vi. Have read and understood the Participant Information Sheet;
vii. Have read, signed and dated the Informed Consent;
viii. Best corrected visual acuity in each eye of at least 20/25
ix. Have normal eyes with the exception of the need for visual correction; subjects must be willing to cease contact lens wear for the duration of the study;
x. 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. Use of Benzalkonium Chloride (BAK) preserved eyedrops in the last month;
ii. Use of Optive brand eyedrops in the last month;
[redacted]
iv. Use of systemic or ocular medications for which test products could be contraindicated as determined by the investigator;
v. Monocular participants (only one eye with functional vision).
vi. Subjects unwilling or unable to cease contact lens wear for the duration of the study;
[redacted]
viii. History of herpetic keratitis, ocular surgery or irregular cornea;
ix. Known pregnancy or lactation during the study period;
[redacted]
xi. Participation in any clinical trial within 30 days of the enrolment visit;

5.4 *Premature Withdrawal*

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

i. The participant withdraws his/her consent to be included in the trial;
ii. An adverse event takes place that is considered by the participant 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 must give written consent according to local 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 is used must be approved by both the Sponsor and by the reviewing IEC. The informed consent must 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 authorized delegated member of the investigational staff must explain to potential participants 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 participants will receive. Finally, they will be told that if needed their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations.

The participants 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 must be appropriately recorded by means of the participant's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the participants.

In the event that additional investigators / sites are added to the protocol, the informed consent will be modified to include the Investigator's name, address, phone number and 24-hour emergency number.

6 Study Design & Procedures

6.1 *General Description*

The study will be a conducted as an open label, bilateral, prospective, interventional single arm clinical study, however, the investigator carrying out the tear film kinetics and tissue staining analyses post-hoc will be masked for these activities.

6.2 *Experimental Routine*

The participants will attend a total of three scheduled visits over a five-week period.
i. Enrolment visit;
ii. Baseline / Dispensing visit (7 ± 1 days from enrolment);
ii. One month follow-up visit (30 ± 3 days from dispensing).

The participants will attend an initial Enrolment visit to obtain their informed consent, evaluate their suitability to take part in the investigation and collect their baseline information. The participants who fulfil the investigation inclusion and exclusion criteria will be dispensed with the run-in eyedrops to be used for one

week. Subjects who wear contact lenses will be required to cease wear during this run-in period (and continue to do so for the duration of the study). At the completion of the one-week run-in period the participants will attend the clinic for baseline measurements and dispensing of the study products. The participants will use the study products as per the study protocol for the reminder of the study. The Baseline and One-month visits will be scheduled in the morning. The participants will not take part in any concomitant investigation of any type or take concomitant medications not allowed by the exclusion criteria.

The participants will complete weekly time stamped questionnaires sent in electronic format using [redacted] secure electronic survey software using either a personal computer, Apple Mac, tablet or smart phone to characterise the time scale of the improvement that may be achieved.

Two visual analogue scale questionnaires will be sent on each occasion: one overnight to capture symptomatology upon waking and one late afternoon to be completed prior to sleep to capture daytime and evening symptomatology. In addition, the participants will complete the OSDI questionnaire one and four weeks after test product dispensing.

6.3 *Measures to Avoid Bias*

6.3.1 Randomization

There is no randomization in this study.

6.3.2 Masking

All videos and images will be anonymized and randomized by an unmasked technician prior to analysis. The investigators conducting the post hoc analyses of the Tearscope videos and digital images will be masked with respect to the participant ID and visit.

6.4 *Test Procedures*

6.4.1 Efficacy Procedures

The primary response procedures will be:

i. OSDI questionnaire;
ii. Digital photography of lissamine green staining of the exposed bulbar conjunctiva.

The secondary response procedure will be:

i. VAS comfort & symptomatology questionnaire ;

[redacted]

6.4.2 Safety Procedures

The procedures to monitor safety will be:

i. Identification and prevalence of adverse events;
ii. Measurement of Snellen visual acuity;

iii. Safety ocular integrity (biomicroscopy).

6.4.3 Population Profiling Procedures

The procedures to profile the population key characteristics will be:

i. Demographics and ocular history questionnaire (including concomitant treatment).
ii. OSDI questionnaire.

[redacted]

aire

xiii. Scheduling

[1] The participants will be given full details of the investigation at the time of making the appointment for the enrolment visit. The explanation at the time of the visit will be to reinforce the information given during the initial telephone contact and answer any questions the participants may have.

[redacted]

7 Statistical Analysis and Sample Size Determination

7.1 *Determination of Sample Size*

A sample size of 27 achieves 81% power to detect superiority using a one-sided t-test when the OSDI margin of equivalence is 7.5 and the true difference between the baseline and the follow-up value is 10.0, the data being drawn from a single population with a within participant standard deviation of 5.0 and with the significance level (alpha) of the test being set at 0.050. Based upon the intended cohort sample it is proposed to screen 40 participants to have 35 participants enrolled into the investigational phase at the end of Visit 2 to achieve a cohort of 30 participants completing the study as per the protocol.

7.1 *Statistical Analysis Plan*

All data summaries and statistical analysis will be performed using SPSS Basic, Advanced and Regression modules (IBM SPSS Statistics). Throughout the data analysis the results for each participant/eye will be used when available.

Summary tables (descriptive statistics and/or frequency tables) will be produced for all the variables recorded. The variables will be summarized by the following statistics:

i. Parametric variables: n, mean, standard deviation (SD), median, minimum and maximum;
ii. Non-parametric variables: n, median, mode, minimum, maximum and categorical distribution.

A detailed statistical analysis Plan (SAP) will be developed as a start-up document prior to database closure and subsequent analysis will include comparative statistics for all primary and secondary variables.

All participants who meet the eligibility criteria, adhere to the protocol, and successfully complete the full study assessment will be available for the per-protocol analysis. Participants with missing data will be included in the analysis unless there is some non-response-related reason to exclude them, such as a protocol violation/invalid data.

8 Risk Analysis

OCULAR TECHNOLOGY GROUP - *International* has conducted an analysis of the benefits and risks of this study. OCULAR TECHNOLOGY GROUP - *International* has determined that this clinical investigation is justified as the overall potential benefit to the population outweighs its risks.

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 new dry eyes management 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 eyedrops products at no cost to them.

8.2 *Risks*

All the assessments are routine clinical procedures or specialized procedures and none present any increased risk to participants compared with normal clinical routine. The risks associated with using the study products are similar to those of using any approved eyedrops for similar indication, such as the participants' own eyedrops. These may include eye irritation, burning and discomfort, eye pain and eye irritation, visual disturbance. Less common side effects include allergic reactions (including eye allergy), blurred vision, sticky eye, watery eye, redness of the eye, eye injury to the surface of the eye due to tip of bottle touching the eye during use.

Since all participants will be dry eyes sufferers, the risks of taking part in the study are no greater than those associated with doing nothing or continuing to use their habitual eyedrops. In addition, this is a five-week study and participants will be under the care of the research investigators closely while they are using the study products and their eyes will be examined at one week and one month post enrolment.

9 Adverse Events and Reporting

9.1 *Adverse Events*

Adverse events including serious adverse events and quality complaints will be reported in accordance with MEDDEV 2.12.1 rev 8 Guideline on a Medical Devices Vigilance System.

9.1.1 Adverse Event Definitions

An **Adverse Event (AE)** is defined in accordance with ISO 14155 as "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device." This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.

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.

All adverse events and clinically significant abnormal laboratory findings will be documented on the CRF.

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."

9.2 *Procedures for Adverse Events*

Treatment of an adverse event will depend on its nature and severity. Based upon 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 eyedrops 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.

9.3 *Reporting Adverse Events*

All safety events and device deficiencies, regardless of causality, will be reported to the principal investigator within 24 hours of the investigator becoming aware of the event.

All SAEs and SADEs occurring during the study period (from signing ICF) through the last subject visit are to be immediately reported to Allergan at a fax number/email address listed on the cover page and recorded on the appropriate eCRFs within 24 hours of awareness. All subjects with an SAE/SADE must be followed up and the outcomes reported. The principal investigator is to supply Allergan and the Independent Ethics Committee with any additional requested information (e.g. hospital discharge summary, autopsy reports and terminal medical reports). Allergan shall evaluate all SADEs and determine and document in writing whether they meet the definition of a UADE. These shall be reported to all participating principal investigators, the regulatory authorities, and IRBs/ECs as required by national regulations.

In the event of an SAE/SADE, the principal investigator must:

1. Notify Allergan immediately by fax/e-mail using the SAE/SADE reporting forms.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Provide Allergan with a complete, written case history which includes a statement as to whether the event was or was not related to the use of the investigational device.

   Promptly inform the Independent Ethics Committee of the event, if it is treatment-related. For other SAEs, notify the Independent Ethics Committee as required by local regulations, and the governing health authorities.

9.4 *Pregnancy*

If a female becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan. The pregnancy reporting form, which contains details of where to send the report, can be found in Appendix B.

10 Device Deficiencies

A device deficiency is defined in accordance with ISO 14155 as “inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.” Device deficiencies include malfunctions, use errors, and inadequate labelling. If a device deficiency occurs, the principal investigator will notify Allergan within 24 hours using the fax number or email on the front page of the protocol. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

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 should

be appropriately qualified and legally entitled to practice, and be 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 Ethics Committee / IRB approval is received prior to the start of the clinical trial, that the Ethics Committee / IRB 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 / IRB and review written approval prior to implementation.

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, 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 same or, in the instance of electronic data, an audit trail must 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. The Sponsor will, 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 specialising 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.

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

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. 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. time stamped, secure electronic survey software will be used to weekly remotely collect the participants 'subjective impression. 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*

The Sponsor 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 be laid out in the Protocol Specific Monitoring Plan (PSMP), which includes:

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. Addressing study issues at the site that may arise with site personnel and/or study team;
vi. Reviewing the study records to ensure completeness and accuracy;
vii. Study and patient 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 as per the PSMP 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 eyedrops shipping orders, dispensing logs and the physical count and disposition of the remaining unused study eyedrops. The clinical monitor will ensure product is reconciled and any discrepancies are investigated and either corrected or documented. At study conclusion, all study eyedrops 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*

The study is an open label study. The only documents that will be masked will be the digital videos of the tear film and the digital photos of the ocular tissues. Masking will only take place post hoc for the purpose of carrying out the analysis in an unbiased manner. Once the analysis is complete unmasking will be implemented. Masking in this study, therefore does not interfere with the participants' safety management.

[redacted]

13 Administration 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)), 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.

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:

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:
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, the Sponsor 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 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. 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 Site Investigators 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.

13.8 *Study Registration*

Since this study is an interventional clinical study, it is considered as an applicable clinical trial for clinical trials registry (www.ClinicalTrials.gov or equivalent); the National Research Ethics Service (NRES) requires that clinical investigations involving medical devices are registered on a publicly accessible register in compliance with the HRA registration requirements for the UK. Therefore, the study will be registered with www.ClinicalTrials.gov. The National Research Ethics Service (NRES) will also publish the research summary wording that is submitted on the Integrated Research Application System (IRAS) Research Ethics Committee Application Form.

13.9 *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 prior written permission of the Sponsor.

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13.11 *Indemnity*

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.

14 References

1. Bitton E, Keech A, Jones l, Simpson T. Subjective and Objective Variation of the Tear Film Pre- and Post-Sleep Optom Vis Sci. 2008. 85: 740–744
2. Dumbleton KA, Guillon M, Theodoratos P, Patel T. Diurnal Variation in Comfort in Contact Lens and Non-contact Lens Wearers. Optom Vis Sci 2016. 93: 820 - 827
3. Lemp MA, Baudoin C, Baum J et al. The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop. Ocular Surface. 2007. 5: 75 – 92

- ISO 14155:2011(E) Clinical investigation of medical devices for human participants – Good clinical practice
- ISO 19980:2012 (E) Ophthalmic optics – Contact lenses and contact lens care products – Guidance for clinical investigations
- MEDDEV 2.12/1 Rev 8 - Guidance document - Market surveillance - Guidelines on a Medical Devices Vigilance System
- International Conference on Harmonization (ICH), Guideline for Good Clinical Practice (GCP)
- Code of Federal Regulations: 21CFR11 (Electronic Records; Electronic Signatures), 21CFR50 (Protection of Human Participants), 21CFR56 (Institutional Review Board), 21CFR812 (Investigational Device Exemptions), 21CFR54 (Financial Disclosure by Clinical Investigators)

15 List of Abbreviations

AE	Adverse Event
BAK	Benzalkonium Chloride
CRO	Contract Research Organization
EC	Ethics Committee
e.g.	For example
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IRAS	Integrated Research Application System
IRB	Investigational Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
mm^2	Millimeter square
NRES	National Research Ethics Service
OSDI	Ocular Surface Disease Index
PIS	Participant Information Sheet
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
VAS	Visual Analog Scale

16 Appendices

16.1 *Appendix A:*

INTERVENTIONAL STUDY: SERIOUS ADVERSE EVENT FORM FOR CLINICAL TRIALS

[redacted]

16.2 *Appendix B:*

CLINICAL TRIAL PREGNANCY REPORT FORM

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