PROTOCOL RE-015B

A 3-MONTH, PROSPECTIVE, MULTICENTRE, INVESTIGATOR-MASKED, PARALLEL-GROUP, ACTIVE-CONTROLLED, RANDOMISED, NON-INFERIORITY STUDY IN ADULT PATIENTS WITH MODERATE-TO-SEVERE DRY EYE DISEASE RELATED TO KERATITIS OR KERATOCONJUNCTIVITIS

THE "ALHENA" STUDY

Sponsor:	SANTEN SAS Genavenir IV, 1 rue Pierre Fontaine F-91058 Evry-Courcouronnes, France
Study Number:	Alhena RE-015B
IND Number:	N/A
ID RCB Number:	2020-A01190-39
Compound:	ALOCROSS® (cross-linked sodium hyaluronate 0.20% and Aloe vera 0.10%)
Date:	Version 2 - 06 July 2020

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the information notice, and any other device information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki (Appendix D).
- International Conference on Harmonisation E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in the Section 11.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I further authorise that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State)

_____
Location of Facility (Country)

_____
Signature of Investigator Date

PROCEDURES IN CASE OF EMERGENCY

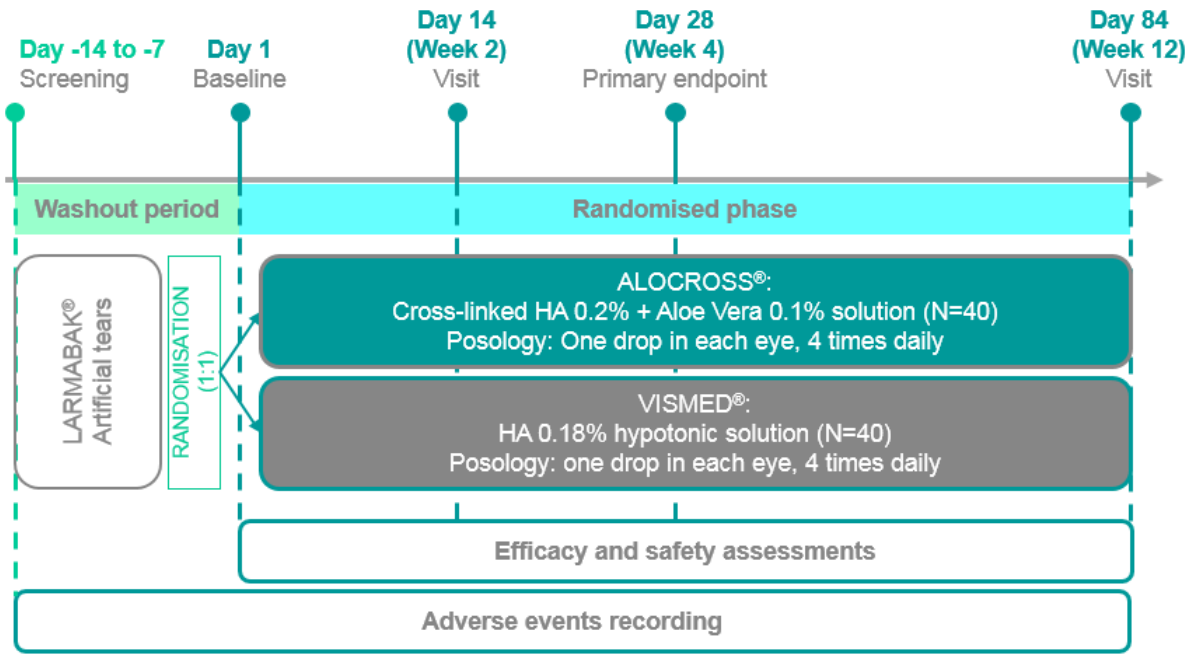
Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical Monitor (Sponsor – Santen)	Filis Ayan Medical Affairs Manager	Santen UK Ltd. Salisbury Hall, St Albans, AL2 1BU, United Kingdom Email: filis.ayan@santen.com Tel. +447483081791
Safety Vigilance Unit (Sponsor – Santen)	Piritta Maunu Manager, Medical Devices Safety Vigilance	Santen Oy Kelloportinkatu 1 P.O. Box 33, FIN-33101 Tampere, Finland Email: safetyEU@santen.com
Pharmacovigilance Unit – ITEC Services	Stéphanie TAN	ITEC Services 7 avenue Pierre Mendès France, Bat. C, 33270 Floirac - France Email: alhena@itecservices.com Tel. +33 5 57 77 85 00

1. SYNOPSIS

Name of Sponsor/Company: SANTEN SAS, France	
Title of Study: A 3-month, prospective, multicentre, investigator-masked, parallel-group, active-controlled, randomised, non-inferiority study in adult patients with moderate-to-severe dry eye disease related to keratitis or keratoconjunctivitis	
Coordinating Investigators: Pr. Marc Labetoulle, MD, Ophthalmology Department, Bicêtre Hospital, APHP, Le Kremlin-Bicêtre, France	
Studied period (years): Estimated date first patient enrolled: September 2020 Estimated date last patient completed: July 2021	**Phase of development:** IV
Objectives: **Primary:** • To compare the ocular efficacy of ALOCROSS® with that of VISMED® in patients with moderate to severe DED related to keratitis or keratoconjunctivitis after a 4-week treatment period (Day 28). **Secondary:** • To compare the ocular efficacy of ALOCROSS® with that of VISMED® in patients with moderate to severe DED related to keratitis or keratoconjunctivitis over a 12-week treatment period • To evaluate the ocular tolerability and safety of ALOCROSS® versus VISMED® in patients with moderate to severe DED related to keratitis or keratoconjunctivitis throughout the duration of treatment	
Number of patients (planned): 80	
Study centres: Approximately 10 centres in France	
Methodology: Prospective, multicentre, investigator-masked, parallel-group, active-controlled, randomised, non-inferiority study	

Study design



Diagnosis and main criteria for inclusion:

Patient eligibility is determined according to the following inclusion criteria:

1. Male or female patient aged 18 years or above
2. Patient using artificial tears for at least 3 months prior to the Screening visit
3. Patient experiencing at least 2 symptoms of ocular discomfort rated ≥23 mm on the 0 to 100 mm visual analogue scale (VAS) (among itching, eye dryness, sticky feeling, photophobia, pain, burning or stinging, sandy feeling or grittiness, or foreign body sensation) at Screening and Baseline visits
4. OSS score (sum of nasal and temporal interpalpebral conjunctival and corneal vital staining) ≥4 and ≤9 on a modified Oxford scale at Screening and Baseline visits in at least one eye
5. TBUT of ≤10 seconds at Screening and Baseline visits and/or Schirmer's tear test of ≥3 and ≤9 mm/5 min at Screening visit in the same eye that fulfil inclusion criteria #4
6. The patient has signed and dated a written informed consent form prior to the initiation of any study procedures

Any patient who meets any of the following criteria (in any eye) will not qualify for entry into the study:

Ocular:

1. CFS score ≥4 on a modified Oxford scale at Screening and Baseline visits
2. Ocular hypertension or glaucoma requiring IOP-lowering medication(s)

3. History of ocular trauma, infection or ocular inflammatory condition within the last 3 months before the screening visit
4. Severe blepharitis and/or severe meibomian gland disease
5. Filamentary keratitis
6. Any ocular surface anomaly not related to DED
7. Active ocular infection or history of ocular allergy or ocular herpes
8. Patient with only one sighted eye or with a best corrected distance visual acuity ≤1/10
9. Use of any topical ocular treatment other than study device during the study (all non-study topical ocular treatment(s) must be stopped at the screening visit)
10. Onset of lid hygiene (whatever the method) less than 2 months before the Screening Visit
11. Use of topical corticosteroids within one month prior the Screening Visit
12. Use of isotretinoin, ciclosporin, tacrolimus, sirolimus, pimecrolimus or ocular cauterisation procedures within 2 months prior the screening visit and throughout the study
13. Use of VISMED® within 6 weeks prior to the screening visit
14. Refractive surgery (e.g. LASIK, LASEK, PRK) within 6 months and/or any other ocular laser/surgery within 3 months prior to the screening visit and during the study
15. Insertion of temporary punctal plug(s) within 2 months prior to the Screening visit or permanent occlusion of lacrimal puncta on one or both sides
16. Known hypersensitivity to any of the components of the study device or investigational products

Non-ocular:

17. History of severe systemic allergy
18. Systemic disease not stabilised within 1 month prior to the screening visit (e.g. diabetes with glycaemia out of range, thyroid dysfunction) or judged by the investigator to be incompatible with the conduct of the study procedures or the interpretation of the study results
19. Any change of systemic concomitant medication within the month before the screening visit or planned change during the study period, except paracetamol
20. Pregnancy or lactation at the screening and/or Baseline visit.
21. Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomised partner) from the Baseline visit throughout the conduct of the study treatment periods and up to 2 weeks after the study end.

Post-menopausal women (two years without menstruation) do not need to use any method of birth control.

22. Participation in a clinical trial with an investigational substance within the past 30 days prior to Baseline visit.
23. Participation in another clinical study at the same time as the present study

Investigational device, dosage and mode of administration:

Investigational device: ALOCROSS®, cross-linked sodium hyaluronate (0,20%) and Aloe vera (0,10%)

Regimen: Instillation of one drop into both eyes, 4 times daily (morning, noon, afternoon and evening).

Reference therapy, dosage and mode of administration:

Reference Product: VISMED®, sodium hyaluronate (0,18%)

Regimen: Instillation of one drop into both eyes, 4 times daily (morning, noon, afternoon and evening).

Duration of treatment: 84 days

Criteria for evaluation:

Criteria will be evaluated by comparison between the two treatment groups at predefined endpoints and/or in comparing the evolution in each treatment group.

Efficacy:

- Ocular surface staining (OSS) score
- Corneal fluorescein staining (CFS) and clearing
- Tear Break-up time (TBUT)
- Schirmer's test
- Symptoms of ocular discomfort (Visual Analogue scale)
- Quality of life questionnaire: NEI-VFQ-25
- Evaluation of global efficacy by the investigator and by the patient

Safety:

- Adverse event (AE) and Serious AE (SAE)
- Best Corrected Distance Visual Acuity (BCDVA)
- Intraocular Pressure (IOP)
- Local ocular tolerance (slit lamp)

Endpoints:

Primary Efficacy Endpoint:

The primary endpoint of the study is the difference between patients treated with ALOCROSS® and patients treated with VISMED® in the change of ocular surface staining (OSS) score between baseline and D28.

Secondary Endpoints:

Efficacy:

The secondary endpoints are the difference between patients treated with ALOCROSS® and patients treated with VISMED® in:

- The change of OSS score between baseline and D14 and between baseline and D84
- The change of ocular stainings (corneal fluorescein staining (CFS) and clearing and conjunctival staining) between baseline and D28 and between baseline and D84
- The change of symptoms and tear breakup time (TBUT) between baseline and D28 and between baseline and D84
- The change of Schirmer's tear test between baseline and D28 and between baseline and D84
- The overall efficacy evaluation of the investigator after 12 weeks of treatment (84 days)
- The change of subjective assessments evaluation by the patient between baseline and D84

Safety and Tolerability:

The tolerability and safety endpoints will evaluate:

- The number of patients with at least one ocular adverse event (AE) and the number of patients with at least one serious adverse event (SAE)
- The number of ocular AEs and SAEs
- The Best Corrected Distance Visual Acuity (BCDVA) from baseline to D84
- The change in intraocular pressure (IOP)
- The local ocular tolerance

Statistical methods:

Study size

With an alpha risk of 0.025, a power of 90% and a non-inferiority margin of 2 points, a sample-size of 66 patients was found necessary.

Study Eye

The study eye is defined as the eligible eye that fulfils all the criteria listed under the inclusion criteria #4 and #5.

Analysis Populations

- The **Full Analysis Set (FAS)** population consists of all randomised patients who received at least one dose of the study device and had at least one post-baseline sign or symptom assessment of the study eye. This will be the population used for efficacy analyses.
- The **Per-Protocol Set (PPS)** will be a subset of FAS, restricted to the patients who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment.

It will be the analysis population for some sensitivity analyses. The determination of the PPS will be done before unmasking.

- The **Safety population** consists of all patients enrolled who received at least one dose of the study device. It will be the analysis population for safety analyses.

Analysis of Demographics and Baseline Characteristics

Descriptive summaries will be performed for demographic (including age, gender, female patients' menopausal status) and baseline characteristics variables (including time since diagnosis, past surgery or laser treatment in the study eye, and smoking status) by each FAS and safety population.

Analysis of Primary Efficacy Endpoint

An MMRM model will be performed to provide the estimate of the least square (LS) means difference between groups in the change from baseline of the ocular surface staining score after 4 weeks of treatment.

The 95% confidence interval of this difference will then be computed and the upper bound will be compared to the non-inferiority margin (2 points).

Analysis of Secondary Efficacy Endpoint

For FAS population, mean scores of OSS score, CFS, conjunctival fluorescein staining, symptoms of ocular discomfort (VAS), TBUT, Schirmer's test and quality of life (NEI-VFQ) score, and their change from baseline will be summarized by analysis visit. The analysis for FAS population will be conducted by treatment groups.

Analysis of Safety and Tolerability Endpoints

Frequencies and percentages of adverse events (AEs) will be presented as follows: 1) Overall summary; 2) by system organ class and preferred term, 3) by system organ class, preferred term and maximal severity, 4) by system organ class, preferred term and relationship to study devices and study procedure, respectively, and 5) by system organ class, preferred term, maximal severity, and relationship to study devices and study procedure, respectively.

These analyses will be performed for AEs and SAEs, ocular and systemic AEs and SAEs, respectively. Ocular AEs will be summarized for the study eye and the fellow eye separately.

Other parameters of safety assessments (e.g. slit lamp examination, BCDVA, and IOP) will be summarised at each time point of measurement, for the study eye and the fellow eye separately.

Safety and tolerability analysis will be performed on Safety population.

Study duration: 11 months

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	**Explanation**
AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
AT	Artificial Tears
BCDVA	Best Corrected Distance Visual Acuity
CA	Competent Authority
CFB	Change From Baseline
CFS	Corneal Fluorescein Staining
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
eCRF	Electronic Case Report Form
EC	Ethics Committee
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions For Use
IOP	Intraocular Pressure
IWRS/IVRS	Interactive Web Response System/ Interactive Voice Response System
LS	Least square
NEI-VFQ	National Eye Institute Visual Function Questionnaire

Abbreviation or Specialist Term	Explanation
NI	Non-inferiority
OD	Ocular Dexter
OS	Ocular Sinister
OSS	Ocular Surface Staining
PPS	Per Protocol Set
QOL	Quality of Life
RSI	Reference Safety Information
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Effect
SAP	Statistical Analysis Plan
SDU	Single Dose Unit
TBUT	Tear Breakup Time
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

4. INTRODUCTION

Since the 2017 International Dry Eye Workshop (DEWS), the term dry eye disease (DED), also known as keratoconjunctivitis sicca, describes "a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film. This loss is accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (DEWS 2017a (1))". The prevalence of DED ranges from 5% to 50% (DEWS 2017b (2)), and it has become one of the principal causes for ophthalmic consultation.

First-line treatments of dry eye focus on the relief of symptoms of ocular discomfort. One of the most extended treatment is instilling artificial tears onto the eye (Dry Eye Syndrome Guidance, 2016 (3)). A variety of solutions with different compositions are available on the market. Hyaluronic acid is an agent used in some eyedrops because of its water retention and lubricant properties, which allow increasing corneal wettability in dry eye patients (Nakamura, 1993 (4)). Several studies have proved the efficacy of hyaluronic acid in achieving improvement in both ocular discomfort symptoms and ocular signs, with good tolerance (Baeyens, 2012 (5); Vogel, 2010 (6); Brignole, 2005 (7); Sand, 1989 (8)). However, the benefit of using eyedrops containing hyaluronic acid over other artificial tears, including saline has not been largely evidenced (Doughty, 2014 (9)). A recent phase III, randomised, crossover, double-blind study by Pinto-Fraga et al showed that Visaid 0.2% was effective in improving some clinical symptoms and signs in comparison with the use of 0.9% saline solution in mild dry eye patients during a 1-month management period (Pinto-Fraga, 2017 (10)). The most important difference was the significant decrease in corneal and conjunctival staining induced by Visaid 0.2%. Additionally, the safety of the solution was proved.

ALOCROSS® is a lubricating ophthalmic solution, based on cross-linked sodium hyaluronate, formulated for the treatment of ocular discomfort and corneal protection. ALOCROSS® obtained the CE mark on May 2017. In addition to the hyaluronic acid component, ALOCROSS® contains Aloe vera, which has known moisturizing, decongestant and lubricating properties. Aloe vera has also proven to improve visual comfort, to prolong the feeling of freshness and to be useful in case of redness or particularly sensitive eyes, fostering an important and long lasting protective action. A 2012 study by Wozniak et al that tested filtered Aloe vera extract on human corneal cells found evidence that Aloe vera may help reduce eye inflammation and dryness (Wozniak, 2012 (11)). The study also noted that Aloe vera, at low concentrations, did not appear to have a negative effect on eye cells, supporting previous findings involving research on animals.

To our knowledge, no other studies have assessed the efficacy and safety of an ophthalmic solution containing both hyaluronic acid salts and Aloe vera. The aim of this study is to demonstrate that ALOCROSS® is non-inferior in terms of efficacy to VISMED® (sodium hyaluronate) for the treatment of signs and symptoms in patients with dry eye.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objective of the study is to compare the ocular efficacy of ALOCROSS® with that of VISMED® in patients with moderate to severe DED related to keratitis or keratoconjunctivitis after a 4-week treatment period (Day 28).

5.2. Secondary Objectives

The secondary objectives are:

- to compare the ocular efficacy of ALOCROSS® with that of VISMED® in patients with moderate to severe DED related to keratitis or keratoconjunctivitis over a 12-week treatment period (Day 84)
- to evaluate the ocular tolerability and safety of ALOCROSS® versus VISMED® in patients with moderate to severe DED related to keratitis or keratoconjunctivitis throughout the duration of treatment

5.3. Endpoints

5.3.1. Primary Efficacy Endpoint

The primary endpoint of the study is the difference between patients treated with ALOCROSS® and patients treated with VISMED® in the change of ocular surface staining (OSS) score between baseline and D28.

5.3.2. Secondary Endpoints

5.3.2.1. Secondary Efficacy Endpoints

The secondary endpoints are the difference between patients treated with ALOCROSS® and patients treated with VISMED® in:

- The change of OSS score between baseline and D14 and between baseline and D84
- The change of ocular stainings (corneal fluorescein staining (CFS) and clearing and conjunctival staining) between baseline and D28 and between baseline and D84
- The change of symptoms and tear breakup time (TBUT) between baseline and D28 and between baseline and D84
- The change of Schirmer's tear test between baseline and D28 and between baseline and D84
- The overall efficacy evaluation of the investigator after 12 weeks of treatment (84 days)
- The change of subjective assessments evaluation by the patient between baseline and D84

5.3.2.2. Safety and Tolerability Endpoints

The tolerability and safety endpoints will evaluate:

- The number of patients with at least one ocular adverse event (AE) and the number of patients with at least one serious adverse event (SAE)
- The number of ocular AEs and SAEs
- The Best Corrected Distance Visual Acuity (BCDVA) from baseline to D84
- The change in intraocular pressure (IOP)
- The local ocular tolerance

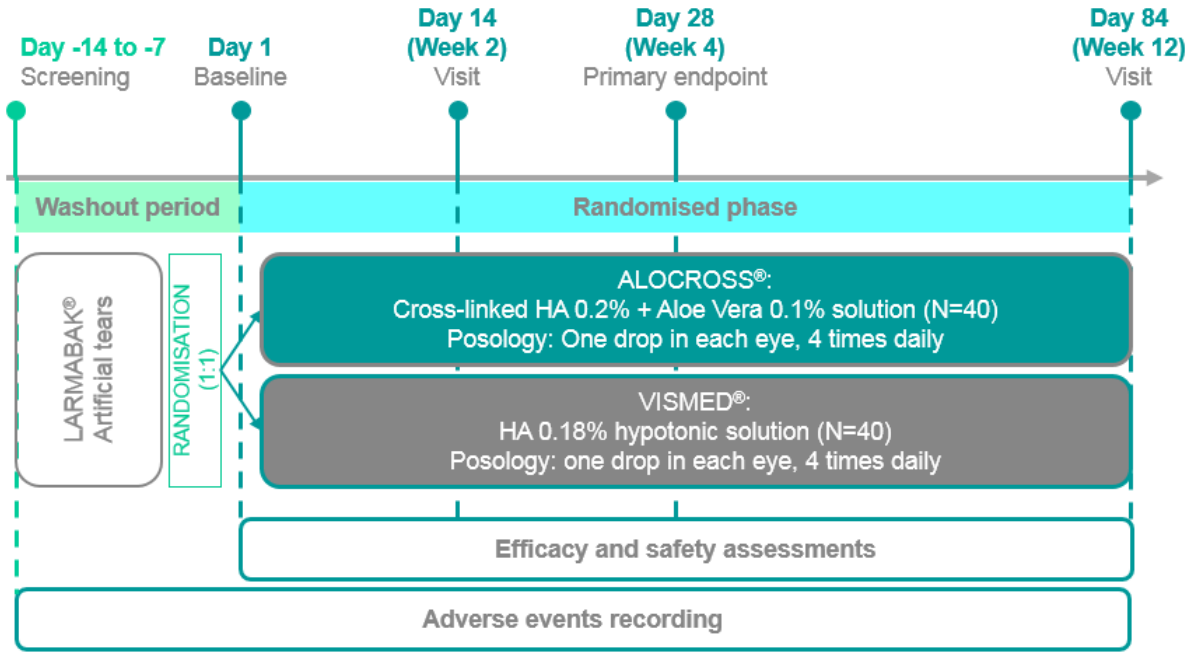
6. INVESTIGATIONAL PLAN

6.1. Study Design

This study is a prospective, multicentre, parallel-group, active-controlled, non-inferiority study conducted in adult patients with moderate-to-severe dry eye disease (DED) related to keratitis or keratoconjunctivitis. This study is conducted at a national level, in France.

The patients will be randomised to receive ALOCROSS® or the reference treatment, VISMED® (ratio 1:1) in an investigator-masked fashion (*Figure **1***).

Figure 1: Study design and schedule of assessments



HA: Hyaluronic Acid

6.2. Number of Patients

A total of 80 patients are planned to be enrolled in approximately 10 trial sites (see section 12.1.1).

6.3. Criteria for Study Termination

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study device that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for patients participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises patient safety.

The Sponsor reserves the right to discontinue the study conduct for any safety, ethical or administrative (force majeure) reason at any time.

If the trial is prematurely terminated or suspended, the Sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The ECs should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

6.4. Demographic, Baseline Characteristics, and Medical History

Demographic information will include demographic characteristics, baseline disease characteristics, age at informed consent, sex and smoking status of the patient at baseline.

Medical history to be obtained will include whether the patient has any significant condition or disease relevant to the condition/disease under study that stopped at or prior to signing the informed consent. Ongoing conditions are considered concurrent medical conditions.

Medication history information to be obtained includes any ophthalmic medication taken within 1 year of signing the informed consent and any other medication stopped at or within 3 months prior to signing the informed consent.

6.5. Schedule of Assessment

Table 3: Study Design and Schedule of Assessments

	Screening Visit	Baseline Visit	Follow-up Visit	Follow-up Visit	End of treatment/end of study visit [a]
	V1	V2	V3	V4	V5
	-14 to -7 days	Day 1	Day 14 ± 3 days	Day 28 ± 7 days	Day 84 ± 14 days
Informed consent	X				
Demographic information	X				
Ocular and systemic medical history	X				
Previous and concomitant ocular and systemic medications	X	X	X	X	X
Review of Inclusion/Exclusion Criteria	X	X			
Symptoms of ocular discomfort: Visual analogue scale	X	X		X	X
Quality of life questionnaire: NEI-VFQ 25		X		X	X
Best corrected distance visual acuity (BCDVA)	X	X		X	X
Slit lamp examination	X	X		X	X
Tear break up time (TBUT)	X	X		X	X
Ocular surface staining score [b]	X	X	X	X (primary endpoint)	X
Schirmer's test (without anesthesia)	X			X	X
Intraocular Pressure (IOP)	X	X		X	X
Urine pregnancy test [c]		X		X	X
Dispensation of unpreserved artificial tears (LARMABAK®)	X				
Randomisation		X			
Investigator and patient global assessment of efficacy			X	X	X
Ocular and systemic adverse events (AEs)		X	X	X	X
Dispensation of masked study device		X		X	
Collection of unused study device containers		X		X	X
Compliance with study device regimen			X	X	X

[a] In case of premature discontinuation, the investigator will perform the final visit of the CRF. It includes all the examinations, if possible.
[b] On modified Oxford scale
[c] For women of childbearing potential only

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Inclusion Criteria

Patient eligibility is determined according to the following criteria:

1. Male or female patient aged 18 years or above.
2. Patient using artificial tears for at least 3 months prior to the Screening visit.
3. Patient experiencing at least 2 symptoms of ocular discomfort rated ≥23 mm on the 0 to 100 mm visual analogue scale (VAS) (among itching, eye dryness, sticky feeling, photophobia, pain, burning or stinging, sandy feeling or grittiness, or foreign body sensation) at Screening and Baseline visits.
4. OSS score (sum of nasal and temporal interpalpebral conjunctival and corneal vital staining) ≥4 and ≤9 on a modified Oxford scale at Screening and Baseline visits in at least one eye.
5. TBUT of ≤10 seconds at Screening and Baseline visits and/or Schirmer's tear test of ≥3 and ≤9 mm/5 min at Screening visit in the same eye that fulfil inclusion criteria #4.
6. The patient has signed and dated a written informed consent form prior to the initiation of any study procedures.

7.2. Patient Exclusion Criteria

Any patient who meets any of the following criteria (in any eye) will not qualify for entry into the study:

Ocular

1. CFS score ≥4 on a modified Oxford scale
2. Ocular hypertension or glaucoma requiring IOP-lowering medication(s)
3. History of ocular trauma, infection or ocular inflammatory condition within the last 3 months before the screening visit.
4. Severe blepharitis and/or severe meibomian gland disease
5. Filamentary keratitis
6. Any ocular surface anomaly not related to DED
7. Active ocular infection or history of ocular allergy or ocular herpes
8. Patient with only one sighted eye or with a best corrected distance visual acuity ≤1/10
9. Use of any topical ocular treatment other than study device during the study (all non-study topical ocular treatment(s) must be stopped at the screening visit)
10. Onset of lid hygiene (whatever the method) less than 2 months before the Screening visit
11. Use of topical corticosteroids one month before the Screening Visit

12. Use of isotretinoin, ciclosporin, tacrolimus, sirolimus, pimecrolimus or ocular cauterisation procedures 2 months before the screening visit and throughout the study
13. Use of VISMED® within 6 weeks prior to the screening visit
14. Refractive surgery (e.g. LASIK, LASEK, PRK) within 6 months and/or any other ocular laser/surgery within 3 months prior to the screening visit and during the study
15. Insertion of temporary punctal plug(s) within 2 months prior to the Screening visit or permanent occlusion of lacrimal puncta on one or both sides
16. Known hypersensitivity to any of the components of the study device or investigational products

Non-ocular

17. History of severe systemic allergy
18. Systemic disease not stabilised within 1 month prior to the screening visit (e.g. diabetes with glycaemia out of range, thyroid dysfunction) or judged by the investigator to be incompatible with the conduct of the study procedures or the interpretation of the study results
19. Any change of systemic concomitant medication within the month before the screening visit or planned change during the study period, except paracetamol
20. Pregnancy or lactation at the screening and/or Baseline visit.
21. Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomised partner) from the Baseline visit throughout the conduct of the study treatment periods and up to 2 weeks after the study end. Post-menopausal women (two years without menstruation) do not need to use any method of birth control.
22. Participation in a clinical trial with an investigational substance within the past 30 days prior to Baseline visit.
23. Participation in another clinical study at the same time as the present study.

7.3. Screen Failure

Investigators must account for all patients who sign the informed consent form. If the patient is found to be not eligible at the Baseline Visit after signing the informed consent, the investigator should complete the eCRF to record the primary reason of failure.

Patient numbers assigned to patients who fail eligibility assessments should not be reused.

Re-assessment is possible. Patients may undergo a new Baseline visit after the signature of a new informed consent form, and a new patient number will be assigned.

7.4. Patient Discontinuation or Withdrawal Criteria

The primary reason for discontinuation or withdrawal of a patient from the study should be recorded in the electronic case report form (eCRF) using the following categories:

1. Adverse event (AE).

   The patient experiences an AE that requires early termination because continued participation imposes an unacceptable risk to the patient's health or the patient is unwilling to continue because of an AE. Patients discontinued for device-related AE(s) will be followed-up after patient's discontinuation until the effect is resolved, stabilized or a final assessment can otherwise be done by the investigator.

2. Protocol deviation.

   The discovery after the administration of the first dose of the study device that the patient failed to meet protocol entry criteria or that the patient did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the patient's health.

3. Lost to follow-up.

   The patient does not return to the clinic and attempts to contact the patient are unsuccessful. In case of a patient lost-to-follow-up, the investigator must do his/her best to contact the patient initially by phone, then by letter, and finally by certified mail. If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or his/her general physician. These attempts must be documented and associated documentation filed in the patient medical chart.

4. Voluntary withdrawal.

   The patient (or patient's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination.

   The Sponsor, EC, or regulatory agency terminates the study.

6. Lack of efficacy.

   The patient or the physician does not feel that the study device has adequately relieved his/her patient's symptoms.

7. Pregnancy.

   The patient is found to be pregnant.

   Note: If the patient is found to be pregnant, the patient must be withdrawn immediately. The procedure is described in Section 7.5.

8. Investigator decision due to non-compliance (to study devices, study visits or study related procedure).

9. Other reason, specify.

Note: All attempts should be made to determine the reason if Other is chosen (e.g. a patient moves to another part of the country, or to a different country, and can no longer be traced) and the specific primary reason should be recorded in the "specify" field of the eCRF.

7.5. Procedures for Discontinuation or Withdrawal of a Patient

The investigator may terminate a patient's study participation at any time during the study when the patient meets one or more of the study withdrawal criteria described in Section 7.4. Efforts should be made to perform all procedures scheduled for the End of Study Visit (D84/End of treatment). Discontinued patients will not be replaced.

7.6. Completed Enrollment

The study enrolment will be considered as completed when the desired number of at least 80 included patients is reached.

7.7. Concomitant Medications/Therapies

Concomitant therapies consist of any treatment or medication given concurrently with the study devices. The following concomitant medication(s)/treatment(s) are prohibited during study participation:

- Use of any artificial tears other than those provided by the Sponsor during the screening period.
- Use of any artificial tears after the Baseline visit
- Use of any topical ocular treatments other than the study devices and preservative-free IOP lowering agents.
- Insertion of temporary punctal plugs during the study.
- Use of any topical corticosteroids after the Baseline visit
- Use of any isotretinoin, ciclosporin, tacrolimus, sirolimus, pimecrolimus or ocular cauterisation procedures after the Baseline visit

The initiation or use during the course of the study of any treatments or procedures described above will be considered as a protocol deviation.

7.8. Randomisation and Masking

The patients who fulfil the inclusion criteria will be randomly assigned (by IWRS/IVRS) in a 1:1 ratio to receive either ALOCROSS® or VISMED® for 12 weeks (84 days) in an investigator-masked fashion.

Each randomised patient will receive numbered study device kits as assigned by the system.

Treatment assignments will be masked to Santen and ITEC employees (except for the Drug Supply personnel), and Investigators. The investigator should try to avoid breaking the masking codes. However**, IN CASE OF EMERGENCY ONLY, (i.e. SERIOUS ADVERSE EVENT [SAE]**

AND ONLY WHEN THIS INFORMATION INFLUENCES THE MANAGEMENT OF THE PATIENT CARE), the investigator is entitled to unmask the patient by using IWRS, in order to obtain the study device information (i.e. ALOCROSS® or VISMED®) to immediately start the appropriate treatment [to be recorded in the source data and eCRF (electronic Case Report Form)]. The date, time and reason for breaking the code will be recorded. The investigator should inform the Sponsor immediately after unmasking. The details of this unmasking procedure will be described in a separate document. Patients unmasked for the management of a SAE will be discontinued from the study.

8. STUDY DEVICE MATERIALS AND MANAGEMENT

8.1. Study Devices

8.1.1. Description of tested device, ALOCROSS®

ALOCROSS® is class IIb medical device and is a lubricant ophthalmic solution based on cross-linked hyaluronic acid 0,20% and Aloe vera gel 0,10% in a buffered solution at pH 7.2.

The batch number and the expiration dates of the study device will be provided in the certificate of analysis.

The legal manufacturer will be OFF Health located in Florence, Italy.

8.1.2. Description of reference treatment, VISMED®

VISMED® is a sterile medical device that contains a preservative-free, drug-free solution of sodium hyaluronate at 0.18%. VISMED® is commonly used as a preservative-free artificial tear treatment in France for patients with keratitis or keratoconjunctivitis. VISMED® will be purchased from a commercial source.

8.1.3. Description of artificial tears, LARMABAK®

LARMABAK® is a sterile unpreserved solution for topical ophthalmic use, containing NaCl at 0.9% (0.9 g/100 mL). LARMABAK® will be purchased from a commercial source.

8.2. Study Device Packaging and Labelling

8.2.1. LARMABAK®

At the screening visit and after review of the selection criteria, selected patients will be provided with 1 bottle of LARMABAK® to perform the wash-out treatment period.

Dosage and mode of administration of LARMABAK®: Instillation of one drop into both eyes, 4 times and up to 8 times daily.

LARMABAK® bottles will bear an investigational label to indicate that the content is intended for investigational use only and to allocate a treatment number to the unit.

8.2.2. Study device

At the Baseline visit (V2), after confirmation of fulfilment of the inclusion criteria and randomisation, the patient will be provided with the study devices (i.e. ALOCROSS® or VISMED®) (see Figure 2)

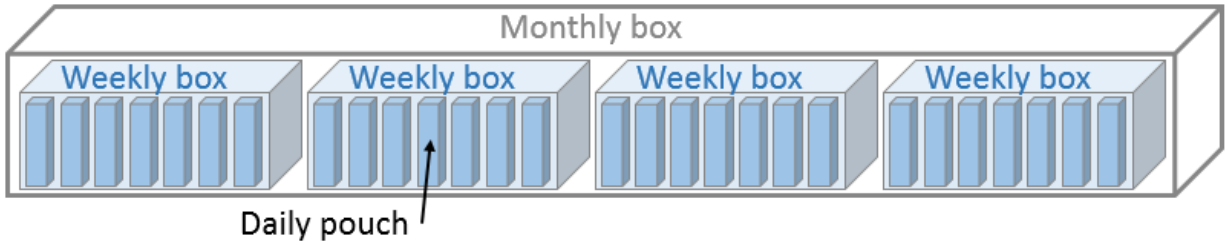
The study devices will be supplied in double-masked polyethylene single-dose unit (SDU) containers presented

- in sealed laminate aluminium pouch package (1 pouch contains 5 single-dose unit containers, sufficient for a one-day treatment of both eyes – daily pouch).
- 7 aluminium pouches (i.e. 35 single-dose unit containers, sufficient for a one-week treatment) will be placed together in a small cardboard box – weekly box.
- 4 cardboard boxes of 7 aluminium pouches (i.e. 140 SDU of study device, sufficient for a 4-week treatment) will be placed together in a large sealed cardboard box – monthly box.

One 'monthly' box of 140 SDU will be dispensed at the Baseline visit.

Two 'monthly' boxes of 140 SDU will be dispensed at the D28 visit.

Figure 2: Study device packaging



8.2.3. Labelling

The single dose containers will not be labelled.

- VISMED® single dose unit containers will receive a blank green sticker to mask the commercial device name.
- ALOCROSS® single dose unit containers will receive a blank white sticker to mask the commercial device name.

Each aluminium pouch and sealed cardboard will bear an investigational label, indicating that the content is intended for investigational use only, the treatment number and the weekday (Monday, Tuesday, …).

In addition, each large cardboard box will bear a white detachable label bearing the protocol and treatment numbers. This label will be torn off by the person dispensing the study device to the patient on Day 1, and stuck onto the space provided in the accountability log.

8.3. Study Device Storage

All clinical trial material must be kept in an appropriate, limited-access, secure location until it is used or returned to the Sponsor or designee for destruction. All study devices must be stored under

the conditions specified on the label, and remain in the original container until it is dispensed. A daily temperature log of the study device storage area must be maintained every working day. Any temperature excursion of study devices should be notified to the Sponsor and the supplies placed in quarantine until further instruction is received from the Sponsor. The study device and unpreserved artificial tears will be delivered to the study centres by the clinical supplies distributor.

The study devices and unpreserved artificial tears must be stored **below 25°C** and must not be frozen. Light exposure must be avoided.

Initially each centre will receive adequate supplies (study devices and unpreserved artificial tears) to cover the study treatment period for a pre-defined number of patients. Additional supplies will be dispatched after taking into account the recruitment rate of each study centre. The investigator or his/her designee will be responsible for correct handling and storage of the study devices and unpreserved artificial tears during the course of the study.

8.4. Administration

The study device will be instilled 4 times daily into both eyes (morning, noon, afternoon and evening).

The study device and the unpreserved artificial tears provided by the Sponsor are to be dispensed only by the investigator or his/her designee, and will be used in accordance with this protocol.

Under no circumstances will the investigator allow the study products to be used other than directed by the protocol. All dispensations and returns of study device have to be documented in the masked pharmacy file provided by the Sponsor (see section 8.5).

In order to ensure patient anonymity, patients will be identified by codes or other means of record identification.

8.5. Study Device Accountability and Destruction

The Principal Investigator has overall responsibility for ensuring that an inventory is conducted upon receipt of the clinical supplies. Due to the study being Investigator Masked, all study device accountability and destruction must be undertaken by the Investigator's unmasked designee. The receipt of clinical supplies should be completed, signed and returned as directed by Santen (or designee). A copy must be maintained at the site for the Investigator's records. The Principal Investigator's unmasked designee will keep a current record of the inventory and dispensing of all study devices. This record will be made available to Santen's Un-masked Monitor (or designee) for the purpose of accounting for all clinical supplies. Any discrepancy and/or deficiency must be recorded with an explanation. All supplies sent to investigator must be accounted for and in no case will study device be used in any unauthorised situation.

It is a responsibility of the Principal Investigator to return any unused supplies to the Santen Un-masked monitor (or designee) at the conclusion of the study.

Patients will be instructed to keep all unused, expired or malfunctioning containers (bottle, SDU and box) and will be required to bring unused, expired or malfunctioning study device containers to each clinic visit. The destruction of the unused, expired or malfunctioning containers of study device will be performed according to the instructions of the clinical monitor and has to be documented.

Upon completion or earlier termination of the study the investigator's unmasked designee will, unless otherwise agreed, return to the clinical supplies distributor any surplus quantities, unused containers/bottles/SDU, of study device or unpreserved artificial tears. The investigator's unmasked designee will record each quantity of study device or unpreserved artificial tears that has been damaged or is missing.

Study device supplies will be counted and reconciled at the site before being returned to Santen or designee or being destroyed by the site.

8.6. Treatment Compliance

Patient compliance will be assessed at each visit by the investigator's unmasked designee by questioning the patient and comparing to study device accountability. All reported lack of compliance will be recorded on the eCRF with the reasons. If a patient is persistently non compliant with the study device, the patient should be withdrawn from the study. All patients should be reinstructed about the dosing requirement at each study visit. The authorized unmasked study personnel conducting the re-education must document the process in the patient source records.

9. SCHEDULE OF OBSERVATIONS AND PROCEDURES

The schedule for all study-related procedures and evaluations is shown in Table 3. Assessments should be completed at the designated visit/time point(s), and should be performed in both eyes.

All assessments should be done in the mentioned order to ensure that additional procedure doesn't interfere with the results of other examinations.

9.1. Screening visit (V1): 14 to 7 days before the Baseline visit

- Written informed consent
- Demographic information
- Ocular and systemic medical history
- Previous and concomitant ocular and systemic medications [including artificial tears (AT) usage]
- Verify inclusion and exclusion criteria based on the evaluations just performed:
    - Patients **fulfilling** the inclusion criteria will discontinue all previous treatments related to dry eye including artificial tears and any prohibited ocular treatments and receive study specific artificial tears for 7 to 14 days
    - Patients **not fulfilling** the inclusion criteria will be considered as having failed the screening and will not be included in the study
- Filling by the patient of the VAS for the symptoms evaluation of ocular discomfort
- BCDVA
- Slit lamp examination

- TBUT
- Ocular surface staining score (corneal fluorescein staining and nasal and temporal interpalpebral conjunctival staining (modified Oxford scale))
- Schirmer's test (without anaesthesia)
- IOP
- Dispensation of unpreserved artificial tears (LARMABAK®)
- Patients will be scheduled to return to the site in 7 to 14 days for the Baseline visit.

9.2. Baseline visit (V2): Day 1

- Collection of the artificial tears bottle
- Inclusion/exclusion criteria review
- Record of previous and concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Record adverse events (AEs)
- Filling by the patient of the VAS for the symptoms evaluation of ocular discomfort
- Completion by the patient of the Quality of life questionnaire NEI-VFQ
- BCDVA
- Slit lamp examination
- TBUT
- Ocular surface staining score (corneal fluorescein staining and nasal and temporal interpalpebral conjunctival staining (modified Oxford scale))
- IOP
- Urine pregnancy test (women of childbearing potential only)
- Randomisation in IWRS
- Dispensation of masked study device for a 4-week period according to the randomisation number
- Patients will be scheduled to return to the site in 2 weeks (Day 14 +/-3 days) for the first follow-up visit (V3)

9.3. Follow-up visit: Visit 3: Day 14

- Record of concomitant ocular and systemic medications
- Record adverse events (AEs)
- Ocular surface staining score (corneal fluorescein staining and nasal and temporal interpalpebral conjunctival l staining (modified Oxford scale))
- Assessment of compliance to study device

- Global assessment of efficacy by the investigator and the patient
- Patients will be scheduled to return to the site in 2 weeks (Day 28 +/-7 days) for the next study visit (V4)

9.4. Follow-up visit: Visit 4: Day 28

- Record of concomitant ocular and systemic medications
- Record adverse events (AEs)
- Filling by the patient of the VAS for the symptoms evaluation of ocular discomfort
- Completion by the patient of the Quality of life questionnaire NEI-VFQ-25
- BCDVA
- Slit lamp examination
- TBUT
- Ocular surface staining score (corneal fluorescein staining and nasal and temporal interpalpebral conjunctival staining (modified Oxford scale))
- Schirmer's test (without anaesthesia)
- IOP
- Urine pregnancy test (women of childbearing potential only)
- Collection of unused, expired or malfunctioning study device containers
- Assessment of compliance to study device
- Global assessment of efficacy by the investigator and the patient
- Dispensation of study device for an 8-week period
- Patients will be scheduled to return to the clinic in 8 weeks (Day 84 +/- 14 days) for the last study visit (V5)

9.5. End of treatment visit/End of study visit: Visit 5: Day 84

- Record of concomitant ocular and systemic medications
- Record adverse events (AEs)
- Filling by the patient of the VAS for the symptoms evaluation of ocular discomfort
- Completion by the patient of the Quality of life questionnaire NEI-VFQ-25
- BCDVA
- Slit lamp examination
- TBUT
- Ocular surface staining score (corneal fluorescein staining and nasal and temporal interpalpebral conjunctival staining (modified Oxford scale))

- Schirmer's test (without anaesthesia)
- IOP
- Urine pregnancy test (women of childbearing potential only)
- Collection of unused, expired or malfunctioning study device containers
- Assessment of compliance to study device
- Global assessment of efficacy by the investigator and the patient

In case of patient's premature study discontinuation:

- the investigator will be asked to perform all the examinations and assessments scheduled for the End of Study Visit

- the investigator will ensure that unused, expired or malfunctioning study devices for the study period has been collected from the patient by the appointed person at the study site

10. ASSESSMENT OF EFFICACY

10.1. Corneal and Conjunctival Fluorescein Staining

Corneal and conjunctival fluorescein staining will be assessed immediately following the TBUT. Reading will be performed between 1 and 4 minutes after fluorescein instillation for the TBUT, to ensure that the dye does not diffuse into stroma blurring the discrete margin of any staining defects. Both eyes will then be examined at the slit lamp (16X magnification) using a yellow barrier filter and cobalt blue illumination to enhance visibility of staining.

Staining using fluorescein will be graded using the modified Oxford scale (7-point ordinal scale, score 0, 0.5, and 1 to 5 per area [cornea + nasal and temporal conjunctiva]) for cornea and conjunctiva separately, see Appendix A-I Modified Oxford Scale. On this modified scale, the score 0 corresponds to no staining dots and the score 0.5 corresponds to one staining dot per area.

A CFS grade of 0 represents complete corneal clearing.

10.2. Tear Break-Up Time

Tear break-up time (TBUT) will be measured by determining the time to tear break-up. The TBUT will be performed after instillation of 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. To thoroughly mix the fluorescein with the tear film, the patient will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TBUT. With the aid of a slit lamp at 10X magnification using cobalt blue illumination, the examiner will monitor the integrity of the tear film, noting the time it takes to form lacunae (clear spaces in the tear film) from the time that the eye is opened after the last blink. The TBUT will be measured twice during the first minute after the instillation of the fluorescein. If the 2 readings differ by more than 2 seconds, then a third reading will be taken. The TBUT value will be the average of the 2 or 3 measurements.

10.3. Schirmer's Test (without anesthesia) (mm wetting/5min)

Schirmer's test will be performed without anesthesia, 15 minutes after corneal fluorescein test. This test will be conducted in a dimly lit room. While the patient looks upwards, the lower lid will be drawn gently downwards and temporally. The rounded bent end of a sterile strip will be inserted into the lower conjunctival sac over the temporal one-third of the lower eyelid margin. The test should be done without touching the Schirmer test strip directly with the fingers to avoid contamination by skin oils. After 5 minutes have elapsed, the Schirmer test strip will be removed and the length of the tear absorption on the strip will be measured.

10.4. Symptoms of ocular discomfort – Visual analogue scale

The visual analogue scale is a self-administered questionnaire and must be completed by the patient him/herself.

Itching, foreign body sensation or sandy feeling or grittiness, photophobia, burning/stinging, eye dryness, pain or ocular discomfort and sticky feeling will be assessed by the study patients using a visual analog scale from no discomfort to maximal discomfort (0 to 100%). Symptoms will be evaluated for both eyes together. (see Appendix A-III Visual Analog Scale (VAS)_Symptoms of Ocular Discomfort).

10.5. Quality of Life Questionnaire: NEI-VFQ-25

The NEI-VFQ-25 is a questionnaire designed to assess health-related quality of life of patients with visual impairments. It is a short-form version of the 51-item NEI-VFQ Field Test Version, composed of 25 items relating to vision–targeted QoL grouped into the following scales: general vision (1 item), ocular pain (2 items), difficulty with near-vision activities (3 items), difficulty with distant-vision activities (3 items), limitations in social functioning due to vision (2 items), mental health symptoms due to vision (4 items), role limitations due to vision (2 items), dependency on others due to vision (3 items), driving difficulties (2 items), limitations with colour vision (1 item), limitations with peripheral vision (1 item), and one widely accepted general health item. Its reliability and validity are comparable to those of the 51-item NEI-VFQ Field Test Version (Mangione, et al 2001).

Each item is scored 0–100, with higher scores indicating better vision-targeted QOL. Items in the same scale are averaged together to create 12 scale scores. Missing items are not scored. A scale score can be generated if at least one item is answered.
The NEI-VFQ-25 represents the patient perspective on the impact of vision problems on functioning. Although not considered to be sensitive to fully capture treatment response in DED, many consider the NEI-VFQ-25 to be the standard to assess vision-targeted functioning.

In this trial the NEI-VFQ-25 will be administered in the local language. The responses to NEI-VFQ-25 are to be obtained from the patient through a self-administered format (see Appendix A-IV National Eye Institute Visual Function Questionnaire (NEI VFQ-25)).

10.6. Investigator and Patient Global Evaluation of Efficacy

The study investigator at each centre will conduct an overall assessment of the effect of the study device on improvement in the patients DED using the following rating scale:

- 0 = Unsatisfactory

- 1 = Not very satisfactory
- 2 = Satisfactory
- 3 = Very satisfactory

The patient will rate his global evaluation of efficacy using the same rating scale.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Best Corrected Distance Visual Acuity (BCDVA)

Best corrected distance visual acuity will be measured with the patient's best correction and recorded in decimal.

11.1.2. Tonometry for measurement of Intraocular Pressure (IOP) (mmHg)

Investigator should use the same tonometer throughout the course of the study. Both eyes will be tested, with the right eye preceding the left eye. IOP will be assessed after completion of all other slit lamp examinations and dry eye assessments to avoid oxybuprocaine interference with the other examinations (Schirmer's test especially) in case a tonometry measurement needs to be performed with an anesthetic.

All tonometers must be calibrated according to manufacturer's instructions. Data need to be measured in absolute figures.

11.1.3. Slit lamp examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp. The patient will be seated while being examined; grading of the Meibomian glands, lids, lashes, conjunctiva, tear film debris, anterior chamber and lens will be done according the scales in Appendix A-II Slit lamp examination.

11.1.4. Adverse Events (AEs)

Adverse events, including ocular AEs, ocular complications, and systemic AEs will be recorded in the eCRFs. Any clinically significant change in concomitant disease or new concomitant conditions will be reported as AEs.

11.1.5. Pregnancy Screen

Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomized partner) from the Baseline visit throughout the conduct of the study treatment periods and up to 2 weeks after the study end cannot be included in the study. Post-menopausal women (two years without menstruation) do not need to use any method of birth control. For women of childbearing potential only, urine hCG pregnancy tests will be performed during the course of the study, and they will receive continued guidance with respect to the avoidance of pregnancy, as part of the Schedule of Study Procedures.

Patients must have a negative urine pregnancy test at baseline.

11.2. Adverse Events and Other Safety Information

11.2.1. Definitions

11.2.1.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Any significant change in a patient's condition from screening, regardless of causality, is to be considered an AE (unless the change is determined to be a continuation of a pre-existing condition documented in the patient's medical history). A clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE.

Worsening of findings e.g. in biomicroscopy from no findings to finding graded as moderate/severe, or change in grading from mild to severe, may be an indication of an AE. By investigator's judgment, also milder changes can be recorded as AEs.

An elective surgical procedure scheduled or planned prior to study entry is not considered an AE, and the underlying diagnosis for the procedure should be captured in the medical history as a pre-existing condition.

The lack of efficacy of the study treatment for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the investigator.

Patients' answers given to study questionnaires (or changes in these) are not reviewed as basis for occurrence of AEs. However, the investigators will collect information on AEs at each patient contact by asking an open question on the patient's general health.

For this study, the study devices are LARMABAK®, ALOCROSS® and VISMED®. Regardless of causality to the study device, an AE can be an unintended sign temporally associated with the use of study device.

11.2.1.2. Device deficiency

Any inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

11.2.1.3. Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device or procedure.

NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2: This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

11.2.1.4. Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without a serious deterioration in health, is not considered a serious adverse event.

11.2.1.5. Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. A SADE is device or procedure related.

11.2.1.6. Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. An USADE is device or procedure related.

NOTE 1: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. The ASADE shall be documented in the CIP, the Instruction For Use (IFU) and the informed consent form.

NOTE 2: This enables compliance with any reporting requirements for anticipated and unanticipated SADEs.

11.2.1.7. Serious Ocular Adverse Events

Serious ocular adverse events include, but are not limited to the following adverse events which are considered to be sight-threatening and are to be reported as SAEs (medically important criteria):

- Adverse Events that cause a decrease in visual acuity > 6 lines (compared with the last assessment of visual acuity at the last visit)
- Adverse Events that cause a decrease in visual acuity to the level of Light Perception or worse
- Adverse Events that required surgical intervention or laser to prevent permanent loss of Sight
- Adverse Events associated with severe intraocular inflammation (i.e. 3+ anterior chamber cell/flare or 3+ vitritis)
- Corneal perforation
- Adverse Events that, in the opinion of the investigator, may require medical intervention to prevent permanent loss of sight

11.2.2. Assessment of Adverse Events

All AEs (non-serious and serious) spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded and assessed during the study at the investigational site. Regardless of relationship to the clinical study, all AEs that occur at any time from the point of signing of ICF to participate in the study until patient withdrawal or the scheduled exit visit must be recorded.

Information about all AEs will be collected from the signing of consent form until the end of the study. Even after completion of the study, the investigator shall notify ITEC services of any new SAEs that may be associated with the study device.

Non-serious AEs will be evaluated until recovery or until the last study visit. The investigator must follow-up with the patients with a SAE until it has resolved, stabilized or a final assessment can otherwise be done. The same principle applies to all study device-related AEs which caused early termination.

The investigator will take appropriate and necessary therapeutic measures required for resolution of the AE. Any medication necessary for the treatment of an AE must be recorded. During the investigator masked treatment period, the investigator should only unmask the treatment allocation if this is relevant to the safety of the patient.

During the study, patients will also be allowed to use unpreserved artificial tears provided by the Sponsor. The events with causal relationship to the artificial tears are considered as AEs.

11.2.2.1. Seriousness assessment

The seriousness of each AE must be assessed by the investigator according to the criteria set for SAEs in section 11.2.1.4. If the event does not meet the criteria of a SAE, it is assessed as non-serious.

11.2.2.2. Causality assessment

An investigator who is qualified in medicine must make the determination of causality to the study devices and artificial tears provided by the Sponsor for each AE occurred during the study as defined in section 11.2.1.1.

The relationship between the use of the medical device (including the medical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the IFU, the Clinical Protocol or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures.

- Not related: relationship to the device or procedures can be excluded when:
    - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has no temporal relationship with the use of the investigational device or the procedures;
    - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
    - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
    - the event involves a body-site or an organ not expected to be affected by the device or procedure;
    - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
    - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
    - harms to the subject are not clearly due to use error;
    - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

- Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explain by another cause, but additional information may be obtained.
- Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
    - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has a temporal relationship with investigational device use/application or procedures;
    - the event involves a body-site or organ that
        - the investigational device or procedures are applied to;
        - the investigational device or procedures have an effect on;
    - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
    - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
    - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
    - harm to the subject is due to error in use;
    - the event depends on a false result given by the investigational device used for diagnosis, when applicable;
    - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of USADE could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

11.2.2.3. Severity of the Adverse Event

Severity (intensity) of the AE will be assessed according to the following scale:

- **Mild:** awareness of sign or symptom, but easily tolerated
- **Moderate:** discomfort sufficient to cause interference with normal activities
- **Severe:** incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.1.4. An AE of severe intensity may not be considered serious.

11.2.2.4. Expectedness

AEs will be evaluated as to whether they are anticipated or unanticipated. The assessment is performed by the sponsor and in this study it is based on the list of adverse device effects in the IFU of ALOCROSS® which acts as a Reference Safety Information (RSI). Only allergic or hypersensitivity reactions to its components may be observed according to the IFU.

- **Expected:** An AE is anticipated when the nature or severity of which is consistent with the applicable product information.
- **Unexpected:** An AE is unanticipated when the nature or severity of which is not consistent with the applicable product information.

11.2.3. Reporting of Safety Information

11.2.3.1. Recording and Reporting of Adverse Events

1. The sponsor or its designee shall fully record all of the following:
   a) any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;
   b) any serious adverse event;
   c) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
   d) any new findings in relation to any event referred to in points (a) to (c).

2. The sponsor or its designee shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following:
   a) Until 25th of May 2021: any serious adverse event with the investigational device, the comparator or the investigation procedure **regardless of relatedness**;
   b) From 26th of May 2021: any serious adverse event that has **a causal relationship** with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
   c) As from 26th of May 2021 follow-up reports for events that have earlier been deemed "not related" are no longer submitted.

d) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

e) any new findings in relation to any event referred to in points (a) to (d).

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor or its designee may submit an initial report that is incomplete followed up by a complete report.

Upon request by any Member State in which the clinical investigation is being conducted, the sponsor or its designee shall provide all information referred to in paragraph 1.

3. The sponsor or its designee shall report any event as referred to in paragraph 2. Upon receipt, this report shall be sent electronically to all Member States in which the clinical investigation is being conducted.

The CRO ITEC Services will record all SAEs and Pregnancy reports and will inform Sponsor about received reports as soon as possible, not later than 1 work day from the first awareness of the event. At the same time, Santen will record any SAEs to Santen safety database. Santen will then perform medical review. ITEC Services will take care of the reporting to EC and CA.

The sponsor is responsible for ongoing safety evaluation of the study device. If there is at least a reasonable possibility that the event is related to the study device and it is both serious and unanticipated (USADE), ITEC services shall initiate expedited reporting, as soon as the medical review is finalized by Santen, according to applicable reporting requirements to all relevant parties, including regulatory authorities and ethics committees. Reporting responsibilities are described in the study specific safety management plan.

Investigators will also be notified of all suspected, unanticipated serious study device –related adverse device effects (USADEs) that occur during the clinical trial.

All serious and non-serious AEs, must be reported on the adverse event electronic case report form (AE e-CRF). In addition, any SAEs, any Device Deficiency that might have led to an SAE if suitable action had not been taken/intervention had not been made/if circumstances had been less fortunate, any new findings/updates in relation to already reported events - must be reported expeditedly to the sponsor (Section 11.2.3.3).

For each AE, the investigator will evaluate and report

- The date site became aware of the event
- The AE/safety information term (verbatim)
- The onset date
- Outcome of event
- The end date, if applicable
- Severity
- Location (e.g. right/left eye, both eyes, or not applicable if non ocular event)

- Causality to study devices (Not related/Unlikely/Possible/Probable/Causal Relationship)
- Causality to artificial tears (Not related/Unlikely/Possible/Probable/Causal Relationship)
- Relationship to study procedures (Not related/Unlikely/Possible/Probable/Causal Relationship)
- Action taken with the study device (for AEs only)
- Seriousness
- Treatment medications, if applicable
- Historical/concurrent medical conditions relevant for the AE
- Whether or not AE caused the patient to discontinue the study.

The AE term should be reported in standard medical terminology when possible.

If known, the diagnosis (i.e., disease or syndrome) must be recorded rather than component signs and symptoms (e.g., record as "worsening of cataract" rather than "drop in vision"). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if worsening of macular edema and worsening of panuveitis are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).

11.2.3.2. Reporting of Pregnancy

Spontaneously reported pregnancy in a patient must be recorded in the source documents at the investigation site and reported expeditedly to ITEC services (Section 11.2.3.3).

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational device may have interfered with the effectiveness of a contraceptive medication. The pregnancy which occurs during the study or within 14 days of completing the study must be reported.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study presuming that the informed consent is obtained for this from the patient. The outcome (health of infant) must also be reported to ITEC services.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.2.3.3. Expedited reporting

The investigator must complete, sign and date the SAE (or Pregnancy) pages, verify the accuracy of the information recorded on the SAE (or Pregnancy) pages, and send a copy by e-mail or fax to ITEC services:

ITEC SERVICES

Email to alhena@itecservices.com **or**

Fax to +33 5 5 77 85 01

(Phone +33 5 5 77 85 00)

The CRO ITEC Services will record all SAEs and Pregnancy reports and will inform Sponsor about received reports as soon as possible, not later than 1 work day from the first awareness of the event. At the same time, Santen will record any SAEs to Santen safety database. Santen will then perform medical review. ITEC Services will take care of the reporting to EC and CA.

Additional follow-up information, if required or available, should all be sent by e-mail or faxed to ITEC Services immediately but no later than within 24 hours of receipt and this should be completed on a follow-up SAE (or Pregnancy) form and placed with the original information and kept with the appropriate section of the eCRF and/or study file.

The sponsor is responsible for ongoing safety evaluation of the study device. If there is at least a reasonable possibility that the event is related to the study device and it is both serious and unanticipated (USADE), ITEC services shall initiate expedited reporting, as soon as the medical review is finalized by Santen, according to applicable reporting requirements to all relevant parties, including regulatory authorities and ethics committees. Reporting responsibilities are described in the study specific safety management plan.

Investigators will also be notified of all suspected, unanticipated serious study device –related adverse device effects (USADEs) that occur during the clinical trial.

11.3. Documentation of Safety Information

All AEs will be recorded during the study in the patient's medical records and on the appropriate AE eCRF at the investigational site. Pregnancies will be recorded in the source documents. The sponsor records all SAEs and Pregnancy reports in the safety database of Santen.

ITEC records all AEs (including SAEs, ADEs etc.) during the study. Santen records all SAEs during the study.

At the end of the study ITEC will send all AEs (including SAEs, ADEs etc.) to Santen.

12. STATISTICS

12.1. General Considerations

Unless specified otherwise, efficacy measures will be summarized by planned treatment, and safety measures will be summarized by actual treatment received. Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%). For the variables recorded for both eyes, the descriptions will be given separately for the study eye and for the fellow eye, when considered relevant.

All data manipulations and descriptive summaries will be performed using SAS Version 9.4 or later.

A Statistical Analysis Plan (SAP) will be written and finalized before the start of the analysis of the study data, which will present the details of how all the analyses will be performed.

12.1.1. Sample Size

The sample size calculation was performed in order to test the non-inferiority of ALOCROSS® versus VISMED®, a commonly used preservative free artificial tear treatment in France for patients with keratitis or keratoconjunctivitis, on the main criterion (ocular surface staining score, the sum of the temporal and nasal interpalpebral conjunctival and corneal fluorescein staining graded using the modified Oxford scale). A standard deviation of 2.5 is expected for this parameter.
With an alpha risk of 0.025 (unilateral test of comparison versus the non-inferiority margin), a power of 90% and a non-inferiority (NI) margin of 2 points, a sample-size of 66 patients was found necessary.

To reach this sample-size in the per protocol population (population of interest in a NI study), a sample-size of 80 patients will be randomised in this study, to allow 15% of patients to be excluded from this population (withdrawals, major deviations…).

12.1.2. Study Eye

The study eye is defined as the eligible eye that fulfils all the criteria listed under the inclusion criteria #4 and #5. If both eyes are eligible, the eye with the highest baseline CFS score will be chosen. If both eyes have the same baseline CFS score, the eye with the lowest Schirmer's test value will be chosen. If both eyes have the same Schirmer's test value, the right eye will be chosen as the study eye.

All the efficacy analyses will be performed on the study eye only.

12.2. Analysis Populations

Analysis populations are defined below:

- The **Full Analysis Set (FAS)** population consists of all randomised patients who received at least one dose of the study device and had at least one post-baseline sign or symptom assessment of the study eye. This will be the population used for efficacy analyses.
- The **Per-Protocol Set (PPS)** will be a subset of FAS, restricted to the patients who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses. The determination of the PPS will be done before unmasking.
- The **Safety population** consists of all patients enrolled who received at least one dose of the study device. It will be the analysis population for safety analyses.

12.3. Analysis of Demographics and Baseline Characteristics

Descriptive summaries will be performed for demographic (including age, gender, female patients' menopausal status) and baseline characteristics variables (including time since diagnosis, past surgery or laser treatment in the study eye, and smoking status) by each FAS and safety population.

In addition, medical history (ocular and systemic) and prior and concomitant medication uses will be summarised. Prior medication is defined as any medication or medical device that was used by the patients that is discontinued before the Baseline visit (Day 1).

12.4. Analysis of Primary Endpoint

The main hypothesis to be tested is the non-inferiority of ALOCROSS® versus VISMED® on the change from baseline (CFB) for the ocular surface staining score, after 4 weeks of treatment:

H0 : (ALOCROSS® CFB – VISMED® CFB) > 2

Ha : (ALOCROSS® CFB – VISMED® CFB) <= 2

An MMRM model will be performed to provide the estimate of the least square (LS) means difference between groups in the change from baseline of the ocular surface staining score after 4 weeks of treatment. This model will include the treatment, visit, and treatment-by-visit interaction as fixed factors, the ocular surface staining score at the baseline and the interaction between the treatment and the ocular surface staining score at baseline as covariates.

The 95% confidence interval (CI) of this difference will then be computed and the upper bound will be compared to the NI margin (2 points). In case where the upper bound will be found less than or equal to the NI margin, the NI of ALOCROSS® versus VISMED® will be demonstrated.

Positive results on the FAS population will be confirmed in the PP population, as for a NI study the two sets of analysis have the same importance (ref. ICHE9).

12.5. Other Efficacy Variables Analyses

12.5.1. Parameters related to the primary criterion

The main model (MMRM) will also be used to analyse the endpoints related to the main criterion (individual components of the ocular surface staining score – nasal and temporal interpalpebral and corneal fluorescein staining scores) after 4 weeks of treatment (28 days).

12.5.2. Other parameters of efficacy

Corneal fluorescein clearing: the number and percentage of patients reaching a score of 0 at their CFS will be presented by group at each time point (week 2, week 4 and week 12), with the corresponding 95% CI ().

Symptoms of ocular discomfort (individual VAS and their mean) will be analysed with an MMRM model using the corresponding baseline value as covariate, at week 2, week 4 and week 12 for the Schirmer test and TBUT at week 4 and week 12.

Evaluation of the efficacy of the treatment by the investigator will be compared between groups at week 2, week 4 and week 12 by a Wilcoxon test.

An exploratory analysis of the NEI-VFQ (QOL Questionnaire) subscale scores and composite score will also be performed. The change from baseline in either total score or appropriate subscale scores will be summarized using descriptive statistics. At week 4, the mean change from baseline will be compared between the groups using an MMRM model with treatment, visit, and treatment-by-visit interaction as fixed effects, baseline value of the corresponding score and the interaction

between the treatment and the ocular surface staining score at baseline as covariates. In order to give more interpretable results, the corresponding LS means will also be expressed in term of effect-size.

12.6. Analysis of Secondary Endpoints

For FAS population, means for OSS score, CFS, conjunctival fluorescein staining, symptoms of ocular discomfort (VAS), TBUT, Schirmer's test and quality of life (NEI-VFQ) score, and their change from baseline will be summarized by analysis visit. The analysis for FAS population will be conducted by treatment groups.

Summary statistics on the scores of Quality of Life variables will be provided as well as their change from baseline at each visit.

Missing data will not be imputed.

12.7. Analysis of Safety and Tolerability Endpoints

All safety and tolerability endpoints analyses will be performed with the Safety population.

12.7.1. Adverse Events

An adverse event is treatment emergent if it occurs or worsens after the first dose of study treatment.

Adverse events will be coded using standard medical terminology. Frequencies and percentages will be given as follows: 1) Overall summary; 2) by system organ class and preferred term, 3) by system organ class, preferred term and maximal severity, 4) by system organ class, preferred term and relationship to study devices and study procedure, respectively, and 5) by system organ class, preferred term, maximal severity, and relationship to study devices and study procedure, respectively.

Separate analyses will be performed for AEs and SAEs, and for ocular and systemic AEs and SAEs, respectively. Ocular AEs will be summarized for the study eye and the fellow eye separately.

12.7.2. Other Safety Assessments

Other parameters of safety assessments (e.g. slit lamp examination, BCDVA, and IOP) will be summarised at each time point of measurement for each safety population. They will be summarised/ analysed for the study eye and the fellow eye separately. The analysis for safety population will be conducted by treatment group.

12.8. Interim Analysis

Not applicable

12.9. Handling of Missing Values

No imputation for missing data will be performed on primary and secondary endpoint analyses. Unless specified otherwise, descriptive summaries will be based on observed cases.

For medical events including AEs, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the Statistical Analysis Plan (SAP). Same rules will be followed to impute the completely or partially missing start and end dates of non-study devices.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will either visit the investigational study site or review the feasibility questionnaire to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Santen SAS or its representatives. This will be documented in a Clinical Study Agreement between Santen or its designee and the investigator.

During the study, a monitor from Santen or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational device accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Santen.
- Confirm non-serious AEs and SAEs have been properly documented on eCRFs and confirm any safety information requiring expedited reporting to ITEC Services (including SAEs and Pregnancies) have been forwarded to ITEC and those SAEs that met criteria for reporting have been forwarded to Santen, to the EC and to the national Competent Authorities.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorised representatives of Santen, a regulatory authority (national or foreign), an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to

systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Santen immediately if contacted by a regulatory agency about an inspection.

13.3. Ethics Committee (EC)

A written favourable opinion of EC (as appropriate) must be obtained before starting the study. Initial EC approval, and all materials approved by the EC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Santen may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an EC. A copy of the letter indicating EC approval or a favourable opinion must be available at the investigational site before the site can enroll any patient into the study.

Any amendment to the protocol must be reviewed by EC in accordance with local requirements. In addition, the EC must approve all advertising used to recruit patients for the study.

Progress reports and notifications of SAEs will be provided to the EC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, ISO 14155:2011 “Clinical investigation of medical devices and applicable regulatory requirements. Please see Appendix D Declaration of Helsinki.

15.3. Written Informed Consent

The Principal Investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The

patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before any protocol-directed procedures are performed.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

In accordance with Act No 78-17 of January 6, 1978 on Information Technology, Data Files and Civil Liberties, the patient will also be informed in writing of his/her right to access, oppose and rectify data recorded in this study.

16. DATA HANDLING AND RECORD KEEPING

16.1. Inspection of Records

Santen or Santen's designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the device storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Ste Agreement between the investigator and sponsor. If it becomes necessary for Santen or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

16.3. Source Documents

The patient source documentation should include hospital reports, doctor's/nurse's notes, laboratory results, reports of special examinations, the signed consent forms, consultants letters. The Investigator is asked to report the following information in the patient's medical file (source documents) according to Sources Data Agreement signed by the Principal Investigator of each Investigational site:

- Mention of patient's participation in the study, patient code and treatment number, date and process of signature of informed consent form
- Demographic data (partial date of birth, sex, name)
- Past medical and surgery history
- Past and recent treatments
- Concomitant treatments at inclusion

- Change in concomitant treatments throughout the study
- Date of each study visit
- Date of the final visit
- Date and reason of premature withdrawal
- All data related to study procedures
- Any non-serious ADEs and SADEs occurred during the time course of the study and study drug-related SAEs which occurred after the completion of the study
- Any pregnancy occurring during the study or within 14 days of completing the study
- Any data that could be judged by the Investigator as relevant

This list is not exhaustive.

16.4. Data Collection

The Principal Investigator must maintain detailed records on all patients who provided informed consent. Data for screened and enrolled patients will be entered into eCRFs, designed according to the protocol. Review of the eCRFs will be completed remotely by Santen (or designee). At designated intervals, a study monitor will perform source data verification on site. During those visits, Santen (or designee) will monitor the patient data recorded in the eCRF against source documents at the study site. Santen (or designee) will review and evaluate eCRF data and use standard system edits, and may use centralised monitoring evaluations, to detect errors in data collection. At the end of the stud, a copy of the completed eCRFs will be sent to the site to be maintained as study records.

17. PUBLICATION POLICY

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Any published data will be written in accordance with prevailing guidelines including International Committee of Medical Journal Editors and Good Publication Practice for Communicating Company-Sponsored Medical Research. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Master Services Agreement or equivalent agreement. In the event of any discrepancy between the protocol and the Master Services Agreement or equivalent agreement the Master Services Agreement or equivalent agreement will prevail.

18. LIST OF REFERENCES

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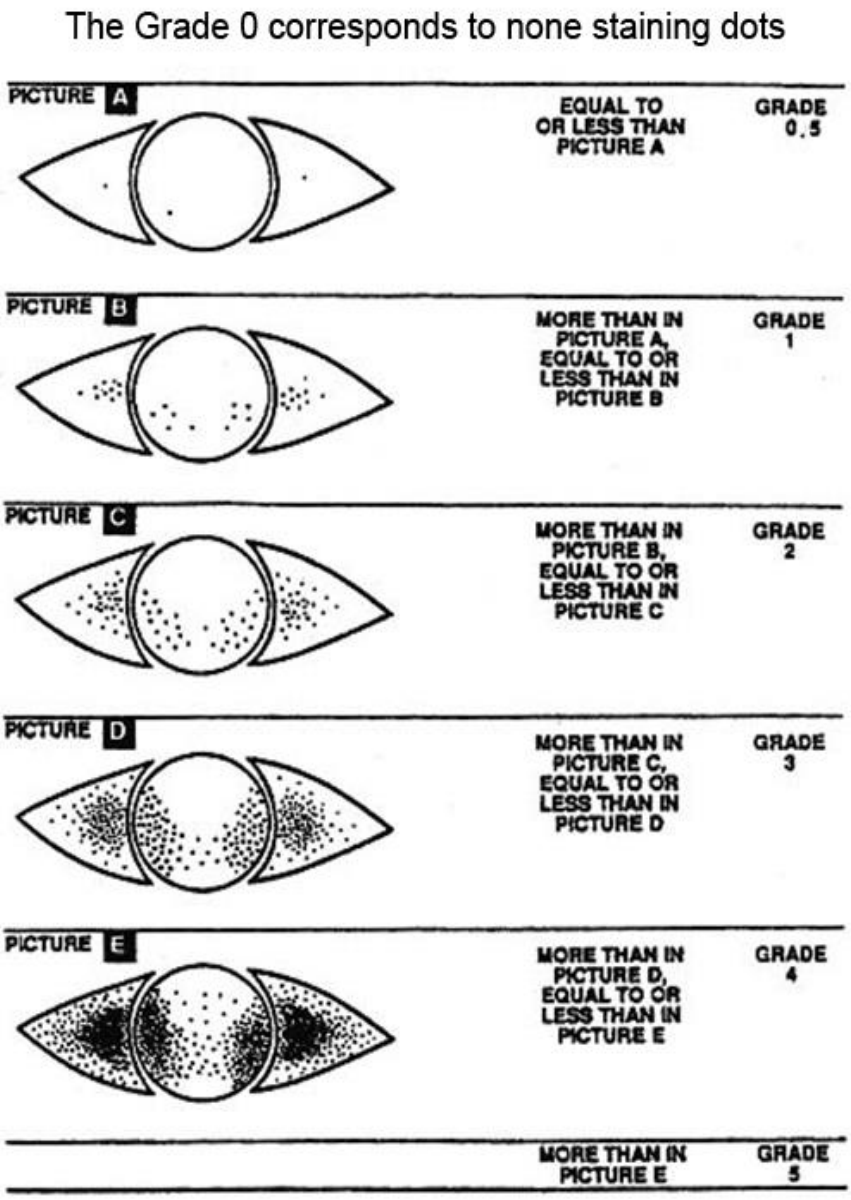
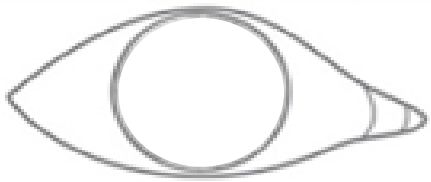
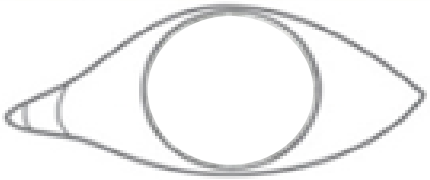
19. APPENDICES

19.1. Appendix A-I Modified Oxford Scale

Grading of corneal fluorescein staining, corneal fluorescein clearing and staining of the nasal and temporal interpalpebral conjunctiva



Grading of corneal fluorescein staining, corneal fluorescein clearing and staining of the nasal and temporal interpalpebral conjunctiva according to the modified Oxford scale.

<table>
<tr><th colspan="3">OD</th><th colspan="3">OS</th></tr>
<tr><td>Temporal interpalpebral conjunctiva</td><td>Corneal area</td><td>Nasal interpalpebral conjunctiva</td><td>Nasal interpalpebral conjunctiva</td><td>Corneal area</td><td>Temporal interpalpebral conjunctiva</td></tr>
<tr><td>A</td><td>B</td><td>C</td><td>C</td><td>B</td><td>A</td></tr>
<tr><td colspan="3">  </td><td colspan="3">  </td></tr>
<tr><td>A</td><td>B*</td><td>C</td><td>C</td><td>B*</td><td>A</td></tr>
<tr><td>0 0.5 1 2
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3 4 5
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<tr><td colspan="3">Ocular Surface Staining Score** = A+B+C =

*If score B ≥ 4, the patient cannot be enrolled
** Patients must have an ocular surface staining score of ≥4 and ≤9 to be enrolled</td><td colspan="3">Ocular Surface Staining Score** = C+B+A =

*If score B ≥ 4, the patient cannot be enrolled
** Patients must have an ocular surface staining score of ≥4 and ≤9 to be enrolled</td></tr>
</table>

Staining scores range from 0-5 for the cornea, temporal and nasal conjunctiva and 0-15 for the total exposed ocular surface.

19.2. Appendix A-II Slit lamp examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp. The patient will be seated while being examined; grading of the Meibomian glands, lids, lashes, conjunctiva, tear film debris, anterior chamber and lens will be done according to the following scales:

Meibomian glands (evaluation of the central ten Meibomian gland openings in the mid-portion of the upper eyelid):

0 = None (none are plugged).
1 = Mild (1 to 2 glands are plugged).
2 = Moderate (3 to 4 glands are plugged).
3 = Severe (All glands are plugged).

Lid - Erythema

0 = None (normal).
1 = Mild (redness localised to a small region of the lid(s) margin OR skin).
2 = Moderate (redness of most or all lid margin OR skin).
3 = Severe (redness of most or all lid margin AND skin).
4 = Very severe (marked diffuse redness of both lid margin AND skin).

Lid - Oedema

0 = None (normal).
1 = Mild (localised to a small region of the lid).
2 = Moderate (diffuse, most or all lid but not prominent/protruding).
3 = Severe (diffuse, most or all lid AND prominent/protruding).
4 = Very severe (diffuse AND prominent/protruding AND reversion of the lid).

Lashes

0 = Normal
1 = Abnormal (specify)

Conjunctiva – Erythema

0 = None (normal).
1 = Mild (a flush reddish colour predominantly confined to the palpebral or bulbar conjunctiva).
2 = Moderate (more prominent red colour of the palpebral or bulbar conjunctiva).
3 = Severe (definite redness of palpebral or bulbar conjunctiva).

Conjunctiva - Oedema

0 = None (normal).
1 = Mild (slight localised swelling).
2 = Moderate (moderate/medium localised swelling or mild diffuse swelling).
3 = Severe (severe diffuse swelling).
4 = Very severe (very prominent/protruding diffuse swelling).

Tear Film Debris

0 = None (absence of debris).
1 = Mild (presence of debris in inferior tear meniscus).
2 = Moderate (presence of debris in inferior tear meniscus and in tear film overlying cornea).
3 = Severe (presence of debris in inferior tear meniscus and in tear film overlying cornea. Presence of mucus strands in inferior fornix of on bulbar conjunctiva).
4 = Very severe (presence of debris in inferior tear meniscus and in tear film overlying cornea. Presence of numerous AND/OR adherent mucus strands in inferior fornix and on bulbar conjunctiva or filamentary keratitis).

Anterior Chamber Inflammation

0 = None (no Tyndall effect).
1 = Mild (Tyndall effect barely discernible).
2 = Moderate (Tyndall beam in the anterior chamber is moderately intense).
3 = Severe (Tyndall beam in the anterior chamber is severely intense).

Lens

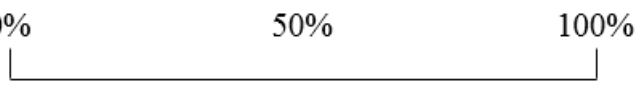
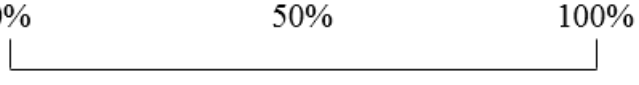
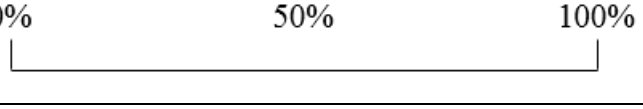
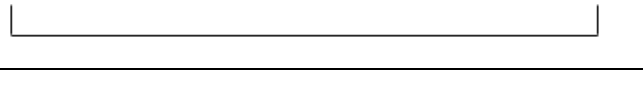
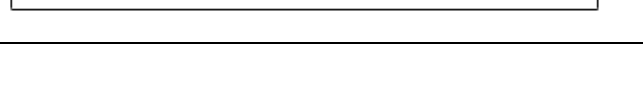
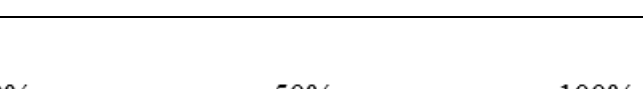
0 = No opacification (normal lens).
1 = Mild lens opacification.
2 = Moderate lens opacification.
3 = Severe lens opacification.

19.3. Appendix A-III Visual Analog Scale (VAS)_Symptoms of Ocular Discomfort

The patient will be asked to assess each symptom regarding ocular discomfort unrelated to instillation among a list of 7 symptoms, i.e. itching, foreign body sensation or sandy feeling or grittiness, photophobia, burning/stinging, eye dryness, pain or ocular discomfort and sticky feeling. The patient will be asked to rate each ocular symptoms by placing a vertical mark on the horizontal line to indicate the level of each ocular symptoms.

0% corresponds to 'no discomfort" and 100% corresponds to "maximal discomfort".

The response will be measured in % between 0 – 100%, on a 100 mm line.

Itching	
Foreign body sensation or sandy feeling or grittiness	
Photophobia	
Burning/stinging	
Eye dryness	
Pain or ocular discomfort	
Sticky feeling	

19.4. Appendix A-IV National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

The NEI-VFQ-25 is self-administered and should be completed by the patient.

PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

English (UK)_Mapi Research Institute_ID2285_Item16a:2980

- 1 - ***version 2000***

The following is a survey with statements about problems which involve your eyesight or feelings that you have about your eye condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. As the purpose of this survey is to improve our knowledge about eyesight problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as if you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they do not apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the centre and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

English (UK)_Mapi Research Institute_ID2285_Item16a:2960

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your health is:**

(Circle One)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. **At the present time, would you say your eyesight in both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor, or are you completely blind?**

(Circle One)

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

English (UK)_Mapi Research Institute_ID2285_Item16a:2980

3. How often are you concerned about your eyesight?

(Circle One)

None of the time..... 1
A little of the time..... 2
Some of the time..... 3
Most of the time 4
All of the time?..... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)?

(Circle One)

None 1
Mild..... 2
Moderate..... 3
Severe 4
Very severe?..... 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for those activities.

5. How much difficulty do you have reading ordinary print in newspapers?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

English (UK)_Mapi Research Institute_ID2285_Item16a:2980

- 4 - ***version 2000***

6. How much difficulty do you have doing work or hobbies that require you to see well close up, such as cooking, sewing, fixing things around the house, or using hand tools?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of shops?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

English (UK)_Mapi Research Institute_ID2285_Item16a:2980

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects on the side while you are walking straight ahead?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

English (UK)_Mapi Research Institute_ID2285_Item16a:2980

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see films, plays or sports events?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

- 7 - ***version 2000***

15. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO: Have you never driven or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF YOU HAVE GIVEN UP DRIVING: Was that mainly because of your eyesight, for some other reason, or because of your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Eyesight and other reasons ..... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

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16. How much difficulty do you have <u>driving at night</u>?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty 4
Have you stopped doing this because of your eyesight..... 5
Have you stopped doing this for other reasons or not interested in doing this 6

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during the rush hour, on the motorway, or in city traffic</u>?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty 4
Have you stopped doing this because of your eyesight?..... 5
Have you stopped doing this for other reasons or are you not interested in doing this? 6

English (UK)_Mapi Research Institute_ID2285_Item16a:2980

PART 3 - RESPONSES TO VISION PROBLEMS

The next questions are about things you may do because of your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like to because of your eyesight?	1	2	3	4	5
18. Are you limited in how long you can work or do your activities because of your eyesight?	1	2	3	4	5
19. How often does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing?	1	2	3	4	5

English (UK)_Mapi Research Institute_ID2285_Item16a:2960

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For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false, or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not sure	Mostly False	Definitely False
20. I stay at home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me.....	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I am concerned about doing things that might embarrass myself or others, because of my eyesight.....	1	2	3	4	5

English (UK)_Mapi Research Institute_ID2285_Item16a:2960

[1]**Development of the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25)** (2001)
Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., & Hays, R. D.
Archives of Ophthalmology, 119, 1050-1058

19.5. Appendix B Elements of the Patient Informed Consent

In seeking informed consent, the following information shall be provided to each patient:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the patient's participation.
- A description of the procedures to be followed, including invasive procedures.
- The identification of any procedures that are experimental.
- The estimated number of patients involved in the study.
- A description of the patient's responsibilities.
- A description of the conduct of the study.
- A statement describing the treatment(s) and the probability for random assignment to each treatment.
- A description of the possible side effects of the treatment that the patient may receive.
- A description of any reasonably foreseeable risks or discomforts to the patient and, when applicable, to an embryo, foetus, or nursing infant.
- A description of any benefits to the patient or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the patient, the patient should be made aware of this.
- Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient and their important potential risks and benefits.
- A statement describing the extent to which confidentiality of records identifying the patient will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- The anticipated prorated payment(s), if any, to the patient for participating in the study.
- The anticipated expenses, if any, to the patient for participating in the study.
- An explanation of whom to contact for answers to pertinent questions about the research (investigator), patient's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the patient.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient otherwise is entitled, and that the patient

may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.
- A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the study.
- The foreseeable circumstances or reasons under which the patient's participation in the study may be terminated.
- A statement that significant new findings developed during the course of the research, which may relate to the patient's willingness to continue participation, will be provided to the patient.
- A written patient authorization (either contained within the informed consent form or provided as a separate document) describing to the patient the contemplated and permissible uses and disclosures of the patient's personal information (including personal health information) for purposes of conducting the study. The patient authorization must contain the following statements regarding the uses and disclosures of the patient's personal information:

a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Santen, its affiliates, and licensing partners; (2) business partners assisting Santen, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer patients the same level of protection as the data protection laws within this country; however, Santen will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

c) that personal information (including personal health information) may be added to Santen's research databases for purposes of developing a better understanding of the safety and effectiveness of the study device(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

d) that patients agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the patient's identity will remain confidential in the event that study results are published.

19.6. Appendix C Investigator Consent to Use of Personal Information

Santen will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, Japan), including the following:

- Santen, its affiliates, and licensing partners.
- Business partners assisting Santen, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Santen and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study device.
- Inspections and investigations by regulatory authorities relating to the study.

Self-inspection and internal audit within Santen, its affiliates, and licensing partners.

- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Santen and other parties for the purposes described above.

19.7. Appendix D Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The

potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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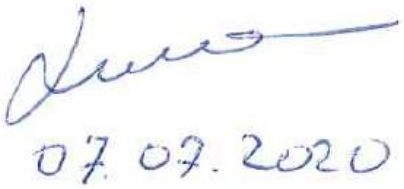
Company/Sponsor signatory **Bogdan Lytvyn, MD, PhD** **Associate Director, Medical Affairs Front of the Eye, EMEA** Office: +41 79 88 59 051	
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