Study Protocol Cover Page

Official Study Title:	A PHASE IV, PROSPECTIVE, OPEN-LABEL, MULTICENTRE, SINGLE ARM, 3-MONTH PROOF OF CONCEPT STUDY TO ASSESS THE EFFECT OF IKERVIS® 1MG/ML (CICLOSPORIN) EYE DROPS ADMINISTERED ONCE DAILY ON THE QUALITY OF VISION IN DRY EYE DISEASE (DED) PATIENTS WITH SEVERE KERATITIS
NCT Number:	NCT03237936
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PROTOCOL

A PHASE IV, PROSPECTIVE, OPEN-LABEL, MULTICENTRE, SINGLE ARM, 3-MONTH PROOF OF CONCEPT STUDY TO ASSESS THE EFFECT OF IKERVIS® 1MG/ML (CICLOSPORIN) EYE DROPS ADMINISTERED ONCE DAILY ON THE QUALITY OF VISION IN DRY EYE DISEASE (DED) PATIENTS WITH SEVERE KERATITIS

Sponsor:	SANTEN SAS Genavenir IV, 1 rue Pierre Fontaine F-91058 Evry, France		
Study Number:	NVG16E128		
IND Number:	N/A	**EudraCT Number:**	2016-003497-40
Compound:	IKERVIS®		
Date:	Version 4.0 23 March 2018 Amendment 2		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

1.2 Approval

REPRESENTATIVES OF SANTEN

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws.

SIGNATURES

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Summary of Product characteristics, and any other product 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.
- International Conference on Harmonisation E6 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 Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.

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

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State)

_____
Location of Facility (Country)

_____
Signature of Investigator Date

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2.0 STUDY SUMMARY

Name of Sponsor(s): SANTEN SAS, France	**Compound:** IKERVIS®	
Title of Protocol: A Phase IV, prospective, open-label, multicentre, single arm, 3-month proof of concept study to assess the effect of IKERVIS® (1mg/ml ciclosporin) eye drops administered once daily on the quality of vision in dry eye disease (DED) patients with severe keratitis.	**IND No.:** NA	**EudraCT No.: 2016-003497-40**
Study Number: NVG16E128	**Phase:** IV	

Study Design:

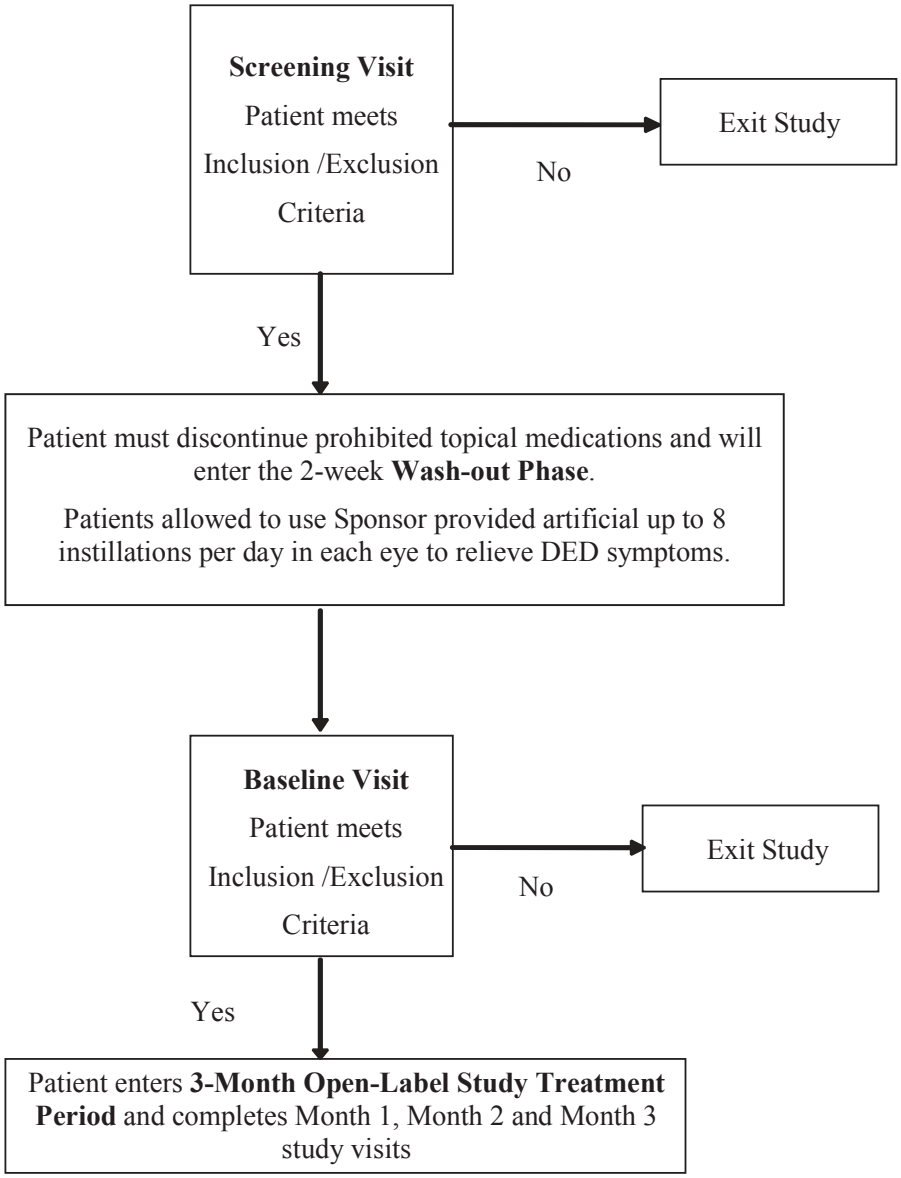
The proposed 3-month study is a prospective, open-label, multicentre, phase IV, proof of concept study. The study is designed to assess the effect on the quality of vision of IKERVIS® (1mg/mL ciclosporin) eye drops administered once daily in dry eye disease (DED) patients with severe keratitis, as well as its safety and efficacy.

Upon completion of the Screening Visit, all enrolled study participants will undergo a 2-week wash-out phase during which prior therapies for DED including artificial tears and prohibited ocular treatments must be discontinued. The purpose of the wash-out phase is to eliminate the potential contribution of any prior DED treatment on the efficacy of the study medication. During the wash-out phase patients may use unpreserved artificial tears provided by the Sponsor as needed in each eye to relieve their dry eye symptoms, up to eight instillations per day. No other topical treatments for DED other than the provided unpreserved artificial tears are allowed during the wash-out phase. Patients will be instructed in the optimal technique for ophthalmic drop instillation.

At the Baseline Visit (Day 1) following the 2-week wash-out phase, patients who meet the inclusion criteria for DED and severe keratitis will start the treatment phase of the study treatment (IKERVIS® 1mg/mL). Patients not fulfilling the inclusion criteria following the wash-out phase will be discontinued from the study without having received the study medication, and will start the best treatment for their condition according to their ophthalmologist's opinion.

During Baseline Visit (Day 1), patients will be instructed to instil one drop of study medication (IKERVIS® 1mg/mL) once daily in each eye at bedtime and will be scheduled for three additional study visits, Month 1 (Day 28±3), Month 2 (Day 56±3), and Month 3 (Day 84±7). In addition to the study medication, patients will also be allowed to use unpreserved artificial tears provided by the Sponsor, up to eight instillations per day, in each eye, to ameliorate their dry eye symptoms. Patients must be instructed not to use artificial tears within 30 minutes before or after use of the study medication and within two hours before a scheduled study visit. All concomitant medications will be recorded on the case report form (eCRF). A change in the use of the study treatments or any use of topical eye drops other than the study medication, sponsor-provided unpreserved artificial tears or topical medications allowed during the study will be considered a protocol violation. In this phase IV clinical trial the Month 3 visit assessments will be used to assess the efficacy (quality of vision and other parameters) and safety of IKERVIS® in DED patients with severe keratitis.

Study Flow Chart



Primary Objective:

To assess the effect on the quality of vision of IKERVIS® (1mg/ml ciclosporin) eye drops administered once daily in adult dry eye disease (DED) patients with severe keratitis following 3 months of treatment, assessed by Functional Visual Acuity (FVA) and Objective Scatter Index (OSI), and to estimate the correlation of the change of Visual Maintenance Ratio (VMR) measured with FVA system and variance of OSI, separately with the expected Corneal fluorescein staining (CFS) improvement.

Secondary Objectives:

- To assess the signs and symptoms of keratitis and DED, and their changes overtime.

<table>
<tr><td colspan="2">

- To estimate the correlation between CFS changes over time and other FVA parameters changes over time.
- To estimate the correlation between CFS changes over time and OSI changes over time.
- To estimate the correlation between variance of OSI changes overtime and FVA parameters overtime.
- To estimate the correlation between OSI changes overtime and FVA parameters changes overtime.
- To compare the time course of the CFS improvement vs the time course of FVA and OSI improvement (if any), respectively.
- To evaluate the ocular tolerability and overall ocular safety of IKERVIS® administered once daily in DED patients with severe keratitis at Month 3.

</td></tr>
<tr><td colspan="2">Patient Population: Adult male or female (aged 18 years or above) DED patients with severe keratitis despite the use of tear substitutes.</td></tr>
<tr><td>Number of Patients: 33 adult patients will be enrolled in the study in order to obtain 30 included patients.</td><td>Number of Sites:
Maximum of 4 sites in France</td></tr>
<tr><td>Dose Level(s):
IKERVIS® (1mg/ml ciclosporin) one drop per day at bedtime at each affected eye</td><td>Route of Administration:
Eye drops</td></tr>
<tr><td>Duration of Treatment:
14 weeks (2-week wash-out period and 12-week treatment period).</td><td>Period of Evaluation:
•Screening/Wash-out: Days -14 (+/- 3 days) to -1.
•Treatment Period 1: Day 1 to Day 84 (+/- 7 days)</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
Male or female DED adult patients with persistent severe keratitis at the Screening and Baseline visits defined as the following: CFS score of 3, 4 or 5 on the modified Oxford scale AND Visual Maintenance Ratio (VMR) <0.95, AND OSI ≥ 2 AND Variance of OSI ≥ 0.5.
A complete list of inclusion criteria is provided in Section 7.1</td></tr>
<tr><td colspan="2">Main Criteria for Exclusion:
Patients presenting with ocular abnormality that may interfere with aberrometry measurement (e.g. macular disease or any loss of transparency of cornea or intraocular structures such as cataract or vitreous hemorrhage) in the eligible eye; or active herpes keratitis or history of ocular herpes. Patients with history of ocular trauma in the eligible eye or ocular infection (viral, bacterial, fungal, protozoal) within 90 days before the Screening Visit in either eye; and any ocular diseases other than dry eye disease requiring topical ocular treatment during the course of the study. Patients with ocular rosacea and/or with severe blepharitis and/or Meibomian Gland Disease (MGD) in the eligible eye. Patients enrolled with mild to moderate blepharitis and/or MGD should be treated as appropriate during the study. Patients with progressive pterygium and/or reaching the optical axis.

A complete list of exclusion criteria is provided in Section 7.2</td></tr>
</table>

Primary endpoint(s) with time point(s) of assessment:

Efficacy endpoints

- Correlation between the change from baseline in VMR measured with FVA system at Month 3 and the change from baseline in the CFS at Month 3.
- Correlation between the change from baseline in variance of OSI measured with double pass aberrometer at Month 3 and the change from baseline in the CFS at Month 3.

Main secondary endpoint(s) with time points(s) of assessment:

Efficacy endpoints

- CFS score assessed with the Modified Oxford Scale and change from baseline at Months 1, 2 and 3.
- FVA parameters (starting visual acuity, FVA, LogMAR FVA, visual maintenance ratio (VMR), and maximal and minimal visual acuities) and their changes from baseline at Months 1, 2 and 3.
- OSI and its variance and their changes from baseline at Months 1, 2 and 3.
- Correlation between CFS changes over time and OSI changes over time and other FVA parameters changes over time, separately.
- Correlation between each OSI parameters changes overtime and FVA parameters changes overtime, separately.
- Root mean square (RMS) of higher order aberrations (total, coma-like, spherical like) measured with Hartmann-Schack aberrometer and their changes from baseline at Month 3.
- Tear Break Up Time (TBUT) and change from baseline at Months 1, 2 and 3.
- Investigator Global Evaluation of Efficacy at Month 3.
- VAS score (photophobia, blurred vision) and changes from baseline at Months 1, 2 and 3.
- Patient Global Evaluation of Efficacy at Month 3.
- Artificial Tear use and change from baseline at Months 1, 2 and 3, and changes from baseline.

Safety evaluations:

- Slit lamp examination and change from baseline at Months 1, 2 and 3.
- Dilated Fundus Examination and change from baseline at Month 3.
- Uncorrected Distance Visual Acuity (UDVA) and change from baseline at Months 1, 2 and 3.
- Best Corrected Distance Visual Acuity (BCDVA) and change from baseline at Months 1, 2 and 3.
- IOP and change from baseline at Month 3.
- Incidence and severity of ocular and systemic adverse events over the study period.

Statistical Considerations:

Sample Size Calculations

In this pilot proof of concept study, no sample size calculation was performed. In order to obtain 30 included patients, 33 patients will be enrolled.

Main efficacy analysis

All the efficacy analysis will be performed on the analysis eye, which is defined as the eligible eye, the eye that fulfils all the criteria listed under the inclusion criteria #4. If both eyes are eligible, the eye with the highest baseline CFS score will be chosen. If both eyes have the same CFS score, the eye with the lowest VMR will be chosen. If VMR values are the same for both eyes, the right eye will be chosen.

Spearman's coefficient of correlation will be calculated at Month 3 between the change from baseline of CFS and respectively the change from baseline of VMR and of variance of OSI.

Secondary and other efficacy endpoints

A mixed effects model will be employed to investigate the association between the change of CFS vs. change of VMR and change of CFS vs. change of OSI, respectively, during the course of the study (from baseline to M3).

Changes in VMR and OSI will also be summarized by categorical change in CFS (-5, -4.5, -4, -3.5, -3, -2.5, -2, -1.5, -1, 0, +1 unit change) and by analysis visit (M1, M2, M3).

Spearman's coefficient of correlation will be calculated at each time-point (M1, M2, M3) between the change from baseline of CFS and respectively the change from baseline of FVA parameters and the change from baseline of OSI parameters.

Spearman's coefficients of correlation will be also calculated at each time-point (M1, M2, M3) between the change from baseline of OSI and of variance of OSI separately and the change from baseline of each FVA parameters.

The graphical curve (with means and error bars at each visit) of each parameter (CFS score, FVA parameters, OSI, variance of OSI) will be generated to explore their pattern of evolution over time (from baseline to M3) under the IKERVIS® treatment.

The other efficacy endpoints will be presented with descriptive statistics at each time-point and in term of change from baseline. The coefficient of variation will be calculated for each criterion in order to provide reliable information on their metric interest for a further study.

Safety analyses

Safety variables recorded in both eyes will be summarized / analysed for both the analysis eye and the other eye separately.

Descriptive statistics will be provided at each time-point concerning the local tolerance parameters.

Usual tables will be produced concerning adverse events (ophthalmic adverse events will be tabulated separately).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities (template). The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Santen SAS will select a Signatory Principal Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	Adverse Event
ATC	Anatomical-Therapeutic-Chemical
BAK	Benzalkonium Chloride
BCDVA	Best Corrected Distance Visual Acuity
BID	Twice a Day
CA	Competent Authority
CFS	Corneal Fluorescein Staining
CKC	Cetalkonium Chloride
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CsA	Ciclosporin/Cyclosporine
D	Day
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
EC	Ethics Committee
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVA	Functional Visual Acuity
g	Gram(s)
GCP	Good Clinical Practice
GRAS	Generally Recognized As Safe
HLA-DR	Human Leukocyte Antigen-DR
IL-2	Interleukin-2
IOP	Intraocular Pressure
KCS	Keratoconjunctivitis Sicca
LogMAR	Logarithm of the Minimum Angle of Resolution
MCT	Medium chain triglycerides
mg	Milligrams(s)
MGD	Meibomian Gland Disease

min	Minutes	
mL	Milliliter	
mm	millimeter	
NF-AT	Nuclear factor of activated T-cells	
OSDI	Ocular Surface Disease Index	
OSI	Objective Scatter Index	
PEO	Polyethylene Oxide	
PPO	Polypropylene Oxide	
PSF	Point Spread Function	
PTE	Pre-Treatment EventQD	Once a Day
RMS	Root Mean Square	
SAE	Serious Adverse Event	
SPK	Superficial Punctuate Keratopathy	
SUSAR	Suspected Unexpected Serious Adverse Reaction	
TEAE	Treatment-Emergent Adverse Event	
TBUT	Tear Break Up Time	
USA	United States of America	
VA	Visual Acuity	
VAS	Visual Analog Scale	
VKC	Vernal Kerato Conjunctivitis	
VMR	Visual Maintenance Ratio	
WHO DRUG	World Health Organization Drug	

3.4 Corporate Identification

Santen SAS	Genavenir IV 1 rue Pierre Fontaine F-91058 Evry, France

4.0 INTRODUCTION

Since the 2007 International Dry Eye Workshop (DEWS), the term dry eye disease (DED), also known as keratoconjunctivitis sicca, describes "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface (DEWS 2007). It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface". Based on the 2007 DEWS report, the prevalence of DED ranges from 5%-15% in the USA, Australia and Europe, to 30-50% in Asia.

Any abnormality of the ocular surface can trigger disequilibrium of the ocular surface integrity and leads to DED (Labetoulle 2013). This results in a vicious circle (Baudouin 2013) with as many ways to enter as there are causes of destabilization of the ocular surface (Baudouin 2007).The pathogenesis of DED is not fully understood; however inflammation has a prominent role in the development and amplification of the signs and symptoms of DED (Stevenson 2012). DED prognosis shows considerable variance, depending upon the severity of the condition and the severity of the underlying pathology. There are very few approved pharmacological treatments for DED in the world, and patients report using artificial tears on a frequent basis (Kymionis 2008). Most patients have mild-to-moderate complaints and can be treated symptomatically with lubricants for long periods of time.

Patients with more severe conditions of DED such as those with severe keratitis (or Sjögren's syndrome) represent a group of patients with the worse prognosis (AAO 2013) and in need of more effective treatments (Asbell 2010). These DED patients with severe keratitis are trapped in a vicious cycle of inflammation and ocular surface injury with the risk of complications such as keratinization of the ocular surface, the occurrence of corneal scarring, a thinning or corneal neovascularization, sterile or microbial corneal ulcerations with a risk of perforation of the cornea and vision loss is possible (AAO 2013). For these severe diseases, clinical guidelines recommend using anti-inflammatory agents such as ciclosporin A (CsA) when lubricants are inadequate (DEWS 2007).

4.1 Background on IKERVIS®

Santen SAS has developed IKERVIS®, a formulation of CsA 1mg/ml designed to optimise the topical delivery of the drug. IKERVIS® via the centralised procedure was granted a Marketing Authorisation on 2015 March 19, by the European Commission[1] for the once daily treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes. This was the first registration for a treatment which indication covers the need for a treatment of severe keratitis as it is expressed by the use of RESTASIS® beyond its FDA-approved indications when present.

CsA is a lipophilic substance practically insoluble in water which must be administered topically to the eye in lipid based systems such as an oily vehicle (Lallemand 2003).

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002066/human_med_001851.jsp&mid=WC0b01ac058001d124

IKERVIS® combines the anti-inflammatory effect of CsA 0.1% with an innovative cationic emulsion formulation (Novasorb® technology) to effectively deliver the drug with once-daily dosing for the treatment of severe keratitis in dry eye patients. Novasorb® is a cationic emulsion composed of oil nanodroplets stabilized by surfactants and dispersed in an aqueous phase. The mean droplet diameter is smaller than 300 nanometers. When cationic emulsions are instilled in the eye, the positively-charged nanodroplets are attracted to the negatively-charged mucosal cells; as a result the residence time of the drop on the epithelial layer of the eye is prolonged by this electrostatic attraction (Lallemand 2012).

4.1.1 Pharmacokinetics and Safety of Animals

A single dose pharmacokinetic pivotal study in rabbits was in favour of IKERVIS® (also called NOVA22007) 1mg/ml (see SmPC). This result was corroborated by a pharmacokinetic study at steady state following multiple administrations which showed that IKERVIS® 1mg/ml administered once a day (QD) achieved higher concentrations in the cornea than RESTASIS ® (0.05%) administered twice a day (BID) with similar target tissue (cornea and conjunctiva) exposure in rabbits.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, phototoxicity and photoallergy, genotoxicity, carcinogenic potential, toxicity to reproduction and development (see SmPC for detailed information).

Effects in non-clinical studies were observed only with systemic administration or at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use

4.1.2 Clinical Pharmacokinetics and Pharmacodynamics

Formal pharmacokinetic studies have not been conducted in humans with IKERVIS®.

Blood concentrations of IKERVIS® were measured using a specific high-pressure liquid chromatography-mass spectrometry assay.

In order to evaluate a possible systemic exposure to IKERVIS®, blood samples were collected in patients included in the Phase IIa study and in two Phase III clinical studies (SANSIKA and SICCANOVE).

In 374 patients from the two phase III studies, plasma concentrations of ciclosporin were measured before administration and after 6 months (SICCANOVE study and SANSIKA study) and 12 months of treatment (SANSIKA study). After 6 months of ocular instillation of IKERVIS® once per day, 327 patients had values below the lower limit of detection (0.050 ng/mL) and 35 patients were below the lower limit of quantification (0.100 ng/mL). Measurable values not exceeding 0.206 ng/mL were measured in eight patients, values considered to be negligible. Three patients had values above the upper limit of quantification (5 ng/mL) however they were already taking oral ciclosporin at a stable dose, which was allowed by the studies' protocol. After 12 months of treatment, values were below the low limit of detection for 56 patients and below the low limit of quantification in 19 patients. Seven patients had measurable

values (from 0.105 to 1.27 ng/mL), all considered to be negligible values. Two patients had values above the upper limit of quantification, however they were also on oral ciclosporin at a stable dose since their inclusion in the study.

Overall, the use of an ocular CsA emulsion is beneficial as it reduces the systemic toxicity of CsA and increases the concentrations of CsA in the conjunctiva and cornea when compared with systemic administration. While it is possible that systemic absorption of IKERVIS® could occur through the nasal mucosa as a result of the drop being cleared from the ocular surface through the lachrymal draining system, both preclinical and clinical studies have shown a negligible systemic passage of IKERVIS® after topical administration, both in animals and in humans.

No specific pharmacology studies were conducted with IKERVIS® since an adequate model of DED does not exist. However, the pharmacodynamics of ciclosporin has been extensively studied in vitro and in vivo. In patients with dry eye disease, a condition that may be considered to have an inflammatory immunological mechanism, following ocular administration, ciclosporin is passively absorbed into T-lymphocyte infiltrates in the cornea and conjunctiva and inactivates calcineurin phosphatase. Ciclosporin-induced inactivation of calcineurin inhibits the dephosphorylation of the transcription nuclear factor of activated T-cells (NF-AT) and prevents NF-AT translocation into the nucleus, thus blocking the release of pro-inflammatory cytokines such as interleukin-2 (IL-2).

4.1.3 Clinical Experience

The approval by the European Commission of IKERVIS® for the treatment of severe keratitis in DED patients was mainly based on the efficacy and safety of results of two randomised, double-masked, vehicle-controlled clinical studies in adult patients with dry eye disease (keratoconjunctivitis sicca) who met the International Dry Eye Workshop (DEWS) criteria (DEWS 2007).

In the 12 month, double-masked, vehicle controlled, pivotal clinical trial (SANSIKA study), 246 Dry Eye Disease (DED) patients with severe keratitis [defined as a corneal fluorescein staining (CFS) score of 4 on the modified Oxford scale] were randomized to one drop of IKERVIS® or vehicle daily at bedtime for 6 months. Patients randomized to the vehicle group were switched to IKERVIS® after 6 months. The primary endpoint was the proportion of patients achieving by Month 6 at least a two-grade improvement in keratitis (CFS) and a 30% improvement in symptoms, measured with the Ocular Surface Disease Index (OSDI). The proportion of responders in the IKERVIS® group was 28.6%, compared to 23.1% in the vehicle group. The difference was not statistically significant (p=0.326).

The severity of keratitis, assessed using CFS, improved significantly from baseline at Month 6 with IKERVIS® compared to vehicle (mean change from baseline was -1.81 with IKERVIS® vs. -1.48 with vehicle, p=0.037). The proportion of IKERVIS®-treated patients with a 3-grade improvement in CFS score at Month 6 (from 4 to 1) was 28.8%, compared to 9.6% of vehicle-treated patients, but this was a post-hoc analysis, which limits the robustness of this outcome. The beneficial effect on keratitis was maintained in the open phase of the study, from Month 6 and up to Month 12.

The mean change from baseline in the 100-point OSDI score was -13.6 with IKERVIS® and -14.1 with vehicle at Month 6 (p=0.858). In addition, no improvement was observed for IKERVIS® compared to vehicle at Month 6 for other secondary endpoints, including ocular discomfort score, Schirmer test, use of concomitant artificial tears, investigator's global evaluation of efficacy, tear break-up time, lissamine green staining, quality of life score, and tear osmolarity.

A reduction in the ocular surface inflammation assessed with Human Leukocyte Antigen-DR (HLA-DR) expression (an exploratory endpoint), was observed at Month 6 in favour of IKERVIS® (p=0.021).

In the 6 month, double-masked, vehicle controlled, supportive clinical trial (SICCANOVE study), 492 DED patients with moderate to severe keratitis (defined as a CFS score of 2 to 4) were also randomised to IKERVIS® or vehicle daily at bedtime for 6 months. The co-primary endpoints were the change in CFS score, and the change in global score of ocular discomfort unrelated to study medication instillation, both measured at Month 6. A small but statistically significant difference in CFS improvement was observed between the treatment groups at Month 6 in favour of IKERVIS® (mean change from baseline in CFS -1.05 with IKERVIS® and -0.82 with vehicle, p=0.009).

The mean change from baseline in ocular discomfort score (assessed using a Visual Analogic Scale, VAS) was -12.82 with IKERVIS® and -11.21 with vehicle (p=0.808).

In both studies, no significant improvement of symptoms was observed for IKERVIS® compared to vehicle after 6 months of treatment, whether using a VAS or the OSDI.

In both studies one third of the patients in average had Sjögren's syndrome; as for the overall population, a statistically significant improvement in CFS in favour of IKERVIS® was observed in this subgroup of patients.

4.2 Rationale for the Proposed Study

DED symptoms comprise intermittent blurred vision, discomfort during daily activities, or troublesome symptoms of irritation that usually worsened at the end of the day (AAO 2013). However, the symptoms of DED patients with severe keratitis usually correlate poorly with the objective clinical findings such as epithelial defects visible with fluorescein staining (Baudouin 2014). In addition many DED patients complain of fluctuated visual acuity despite normal visual acuity in conventional evaluations (Kaido 2011).

Several technics have been used to assess the impact of the severity of keratitis on patient visual function impairment. In this context, the Functional Visual Acuity (FVA) measurement has been reported to be useful in the assessment of visual quality in DED patients (Goto 2002). FVA is a dynamic assessment of the visual acuity which can ascertain DED patients' performance in relation to certain daily activities involving visual tasks by detecting masked impairment of visual function due to ocular surface conditions (Kaido 2013).

Quality of vision can also be assessed using aberrometry technics which measure the ocular aberrations. One study showed that there is an increase in ocular aberrations as the ocular surface

becomes irregular (Hiraoka 2012). Several studies have shown changes in ocular aberrations between blinks (Albarran 1997, Tutt 2000, Koh 2006). Furthermore, using double-pass aberrometry which allows the objective measurement of high-order optical aberrations and loss of ocular transparency, the variance of the observed Objective Scatter Index (OSI) is an objective way to assess the intensity of the subjective visual disturbances reported by DED patients (Habay 2014). Thus, the impact of the severity of DED on the quality of the vision can be ascertained using these new tools.

During IKERVIS® clinical development, standard visual acuity testing performed in the clinical trials didn't permit to detect any relevant changes on visual acuity. This Proof of Concept study will allow assessing the effect of IKERVIS® on the quality of vision in DED patients with severe keratitis using FVA measurement system and ocular aberrations measurement and to calculate the correlations of these parameters with CFS after 3 months of treatment with IKERVIS®, as well as providing meaningful information about the time course of FVA and ocular aberrations improvement in relation with the improvement of CFS. A phase IIIb study will thereafter be conducted based on the results of this study to expand the indication of IKERVIS® for the treatment of symptoms assessed by functional visual acuity.

4.3 Benefit risk balance

The patients participating in the study will benefit from IKERVIS®, a product marketed for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes. Based on inclusion criteria patients will have visual function deficiencies in addition to severe keratitis and it is expected to be improved with IKERVIS® (main objective of the study). Patients will benefit from a close follow-up by the investigators (every month) which is not the case in the usual clinical practice. The risks related to the participation of the study are the adverse events listed on the SmPC, the potential risk of allergy to fluorescein, anaesthetic eye drops or artificial tears and the potential irritation related to the Schirmer test examination.

In light of the points listed above the benefit risk balance is considered favourable.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

The primary objective of the study is to assess the effect on the quality of vision of IKERVIS® (1mg/ml ciclosporin) eye drops administered once daily in adult dry eye disease (DED) patients with severe keratitis following 3 months of treatment, assessed by Functional Visual Acuity (FVA) and Objective Scatter Index (OSI), and to estimate the correlation of the change of Visual Maintenance Ratio (VMR) measured with FVA system and variance of OSI, separately with the expected Corneal fluorescein staining (CFS) improvement.

5.1.2 Secondary Objectives

The secondary objectives are:

- To assess the signs and symptoms of keratitis and DED, and their changes overtime,
- To estimate the correlation between CFS changes over time and FVA changes over time,
- To estimate the correlation between CFS changes over time and OSI changes over time,
- To estimate the correlation between variance of OSI changes overtime and FVA parameters overtime.
- To estimate the correlation between OSI changes overtime and FVA parameters changes overtime
- To compare the time course of the CFS improvement vs the time course of FVA and OSI improvement (if any), respectively,
- To evaluate the ocular tolerability and overall ocular safety of IKERVIS® administered once daily in DED patients with severe keratitis at Month 3.

5.2 Endpoints

5.2.1 Primary Efficacy Endpoints

- Correlation between the change from baseline in VMR measured with FVA system at Month 3 and the change from baseline in the CFS at Month 3.
- Correlation between the change from baseline in variance of OSI measured with double pass aberrometer at Month 3 and the change from baseline in the CFS at Month 3.

5.2.2 Secondary Endpoints

5.2.2.1 Efficacy Endpoints

- CFS score assessed with the Modified Oxford Scale and change from baseline at Months 1, 2 and 3.
- FVA parameters (starting visual acuity, FVA, LogMAR FVA, visual maintenance ratio (VMR), and maximal and minimal visual acuities) and their change from baseline at Months 1, 2 and 3.
- OSI and its variance and their change from baseline at Months 1, 2 and 3.
- Correlation between CFS changes over time and OSI changes over time and other FVA parameters changes over time, separately.
- Correlation between each OSI parameters changes overtime and FVA parameters changes overtime, separately.
- Root mean square (RMS) of higher order aberrations (total, coma-like, spherical like) measured with Hartmann-Schack aberrometer and their change from baseline at Month 3.
- Tear Break Up Time (TBUT) and change from baseline at Months 1, 2 and 3.
- Patient Global Evaluation of Efficacy at Month 3.
- VAS scores (photophobia, blurred vision) and their change from baseline at Months 1, 2 and 3.
- Investigator Global Evaluation of Efficacy at Month 3.
- Artificial Tear use and change from baseline at Months 1, 2 and 3.

5.2.2.2 Safety Evaluations

- Slit lamp examination and change from baseline at Months 1, 2 and 3.
- Uncorrected Distance Visual Acuity (UDVA) and change from baseline at Months 1, 2 and 3.
- Best Corrected Distance Visual Acuity (BCDVA) and change from baseline at Months 1, 2 and 3.
- Dilated fundus examination and change from baseline at Month 3.
- IOP and change from baseline at Month 3.
- Incidence and severity of ocular and systemic adverse events over the study period.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

The proposed 3-month study is a prospective, open-label, multicentre, phase IV, proof of concept study. The study is designed to assess the effect on the quality of vision of IKERVIS® (1mg/mL ciclosporin) eye drops administered once daily in dry eye disease (DED) patients with severe keratitis, as well as its safety and efficacy.

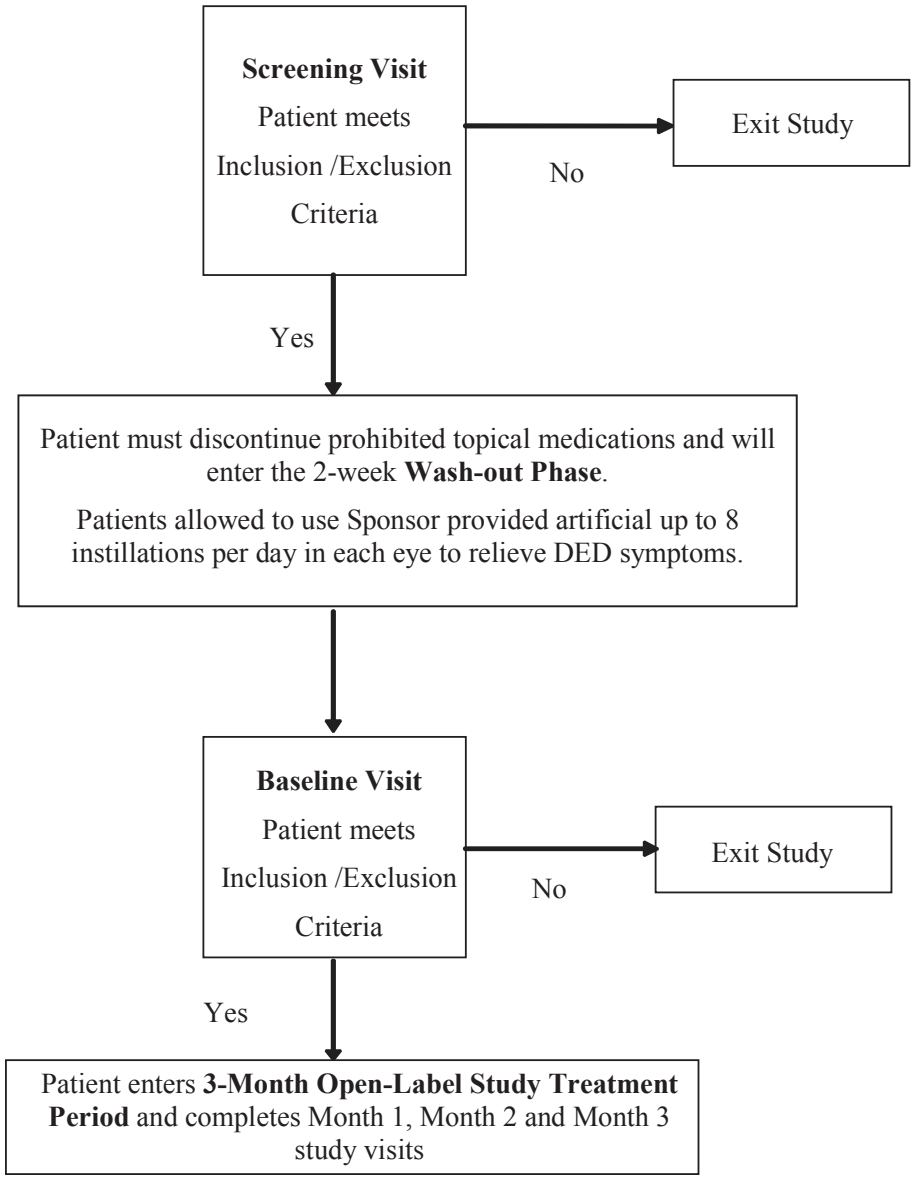
Upon completion of the Screening Visit, all enrolled study participants will undergo a 2-week wash-out phase during which prior therapies for DED including artificial tears and prohibited ocular treatments must be discontinued. The purpose of the wash-out phase is to eliminate the potential contribution of any prior DED treatment on the efficacy of the study medication. During the wash-out phase patients may use unpreserved artificial tears provided by the Sponsor, up to eight instillations per day in each eye, to relieve their dry eye symptoms. No other topical treatments for DED other than the provided unpreserved artificial tears are allowed during the wash-out phase. Patients will be instructed in the optimal technique for ophthalmic drop instillation.

At the Baseline Visit (Day 1) following the 2-week wash-out phase, patients who meet the inclusion criteria for DED and severe keratitis will start the treatment phase with the study treatment (IKERVIS® 1mg/mL). Patients not fulfilling the inclusion criteria following the wash-out phase will be discontinued from the study without having received the study medication.

During Baseline Visit, patients will be instructed to instil one drop of study medication (IKERVIS® 1mg/mL) once daily in each eye at bedtime and will be scheduled for three additional study visits, Month 1 (Day 28 ±3), Month 2 (Day 56±3), and Month 3 (Day 84±7). In addition to the study medication, patients will also be allowed to use unpreserved artificial tears provided by the Sponsor, up to eight instillations per day in each eye, to alleviate their dry eye symptoms. Patients must be instructed not to use artificial tears within 30 minutes before or after use of the study medication and within two hours before a scheduled study visit. All concomitant medications will be recorded on the case report form (eCRF). A change in the use of the study treatments or any use of topical eye drops other than the study medication, sponsor provided unpreserved artificial tears or topical medications allowed during the study will be considered a protocol violation. In this phase IV clinical trial, the Month 3 Visit assessments will be used to assess the efficacy (quality of vision and other parameters) and safety of IKERVIS® in DED patients with severe keratitis.

The study flowchart is illustrated in Figure 1.

Figure 1 Study flow chart



6.2 Justification for Study Design, Dose and Endpoints

Based on development pilot studies, IKERVIS® (CsA 1mg/mL) has been registered in 31 European countries for the indication: treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes, at the recommended dose of one drop of IKERVIS® once daily to be applied to the affected eye(s) at bedtime. During IKERVIS® clinical development, standard visual acuity testing performed in the clinical trials didn't permit to detect any relevant changes on visual acuity. However, the symptoms of DED patients with severe keratitis usually correlate poorly with the objective clinical findings such as epithelial defects visible with fluorescein staining (Baudouin 2014). In addition many DED patients complain of decreased visual acuity despite normal visual acuity in conventional testing (Kaido 2011). Otherwise, several technics have been used to assess the impact of the severity of keratitis on patient visual function impairment. Thus this proof of concept study has been designed to assess the effect on the quality of vision of IKERVIS® (1mg/ml ciclosporin) eye drops administered once daily in adult dry eye disease (DED) patients with severe keratitis following 3 months of treatment, using Functional Visual Acuity (FVA) and Objective Scatter Index (OSI), and to estimate their correlation with the expected Corneal fluorescein staining (CFS) improvement.

6.2.1 Criteria for Premature Termination or Suspension of the Study

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 medication 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.

6.2.2 Criteria for Premature Termination or Suspension of Investigational Site(s)

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.2.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PATIENTS

All entry criteria, including test results, need to be confirmed prior to first dose of study drug on Day 1.

7.1 Inclusion Criteria

Patient eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the patient is capable of understanding and complying with protocol requirements.
2. The patient signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Male or female patient is aged 18 years or above.
4. DED patients with persistent severe keratitis at the Screening and Baseline Visits defined as the following:
   - CFS score of 3, 4 or 5 on the modified Oxford scale

   AND
   - Visual Maintenance Ratio (VMR) < 0.95

   AND
   - OSI ≥ 2

   AND
   - Variance of OSI ≥ 0.5.
5. Patient must be willing and able to undergo and return for scheduled study-related examinations.
6. The same eye (eligible eye) should fulfil all the above criteria.

7.2 Exclusion Criteria

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

1. Any ocular abnormality that may interfere with aberrometry measurement (e.g. macular disease or any loss of transparency of intraocular structures such as cataract or vitreous haemorrhage ….), in the eligible eye.
2. Active herpes keratitis or history of ocular herpes.
3. History of ocular trauma in the eligible eye or history of ocular infection (viral, bacterial, fungal, protozoal) within 90 days before the Screening Visit in either eye.
4. Any ocular diseases other than DED requiring topical ocular treatment during the course of the study.

5. Patients with ocular rosacea and/or with severe blepharitis and/or Meibomian Gland Disease (MGD), in the eligible eye. Patients enrolled with mild to moderate blepharitis and/or MGD should be treated as appropriate during the study.
6. Patients with progressive pterygium.
7. Concurrent ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye.
8. Anticipated use of temporary punctal plugs in the eligible eye, during the study. Patients with punctal plugs placed prior to the Screening Visit are eligible for enrolment; however, punctual plugs must remain in place during the study.
9. Abnormal lid anatomy or blinking function in the eligible eye such as but not limited to entropion, ectropion.
10. Abnormalities of the nasolacrimal drainage system in the eligible eye.
11. Best corrected distance visual acuity (BCDVA) score ≥ +1.0 LogMAR (≤ 35 ETDRS letters, ≤ 20/200 Snellen or ≤ 0.1) in each eye.
12. Use of topical CsA (e.g. IKERVIS®, RESTASIS®), tacrolimus or sirolimus within 90 days before the Screening Visit in the eligible eye. These treatments are also prohibited in both eyes during the course of the study, except IKERVIS® which will be administered as study treatment.
13. Use of topical corticosteroids, antibiotics, pilocarpine, antihistamines, or BAK preserved Intraocular Pressure (IOP) lowering medications within the 30 days before Screening Visit, in the eligible eye.
14. Patients with diffractive multifocal intraocular lenses, in the eligible eye.
15. Any ocular laser/surgery in the eligible eye within 90 days of Screening Visit.
16. Patient refusing to discontinue the use of contact lenses in the eligible eye, during the study.
17. Disease not stabilized within 30 days before the Screening Visit (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections) or judged by the investigator to be incompatible with the study.
18. Presence or history of severe systemic allergy.
19. Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein, etc).
20. History of malignancy in the last 5 years.
21. Any change within 30 days of the Screening Visit or anticipated change during course of the study in the dose of systemic medications that could affect a dry eye condition [mainly, estrogen-progesterone or other estrogen derivatives (only allowed for post-menopausal women), pilocarpine, isotretinoine, tetracycline, antihistamines, tricyclic

antidepressants, anxiolytics, antimuscarinics, beta-blocking agents, phenothiazines, omega-3, systemic corticosteroids]. These treatments are allowed during the study provided they remain stable throughout the course of the study.

22. Any change in systemic immunosuppressant drugs within 30 days before the Screening Visit or anticipated change during the course of the study.
23. History of drug addiction or alcohol abuse.
24. Presence or history of any systemic or ocular disorder, condition or disease that could possibly interfere with the conduct of the required study procedures or the interpretation of study results
25. Pregnancy or lactation at the Screening Visit and/or Baseline Visit.
26. 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 Screening 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.
27. Vulnerable person referring to the French Health legislation « Code de la Santé Publique » articles L.1121-6 and L.1121-8 (patients deprived of liberty due to legal or administrative decision, patients with mental disabilities, patients legally protected or unable to provide their consent).
28. Participation in a clinical trial with an investigational substance within the past 30 days prior to Screening Visit.
29. Participation in another clinical study at the same time as the present study.

7.3 Excluded Medication, Treatments and Procedures

Any patient who uses the following treatment will not qualify for entry into the study.

7.3.1 Ocular Treatments

1. Use of topical CsA (e.g. IKERVIS®, RESTASIS®), tacrolimus or sirolimus within 90 days before the Screening Visit in the eligible eye. These treatments are also prohibited in both eyes during the course of the study, except IKERVIS® which will be administered as study treatment.
2. Use of topical corticosteroids, antibiotics, pilocarpine, antihistamines, or BAK preserved Intraocular Pressure (IOP) lowering medications within the 30 days before Screening Visit in the eligible eye.
3. Patients with diffractive multifocal intraocular lenses in the eligible eye.

4. Any ocular laser/surgery in the eligible eye within 90 days of Screening Visit.
5. Use of any artificial tears other than those provided by the study sponsor during the course of the study i.e. from Screening to Month 3 or Early Termination Visits.
6. Use of any topical ocular treatment in the eligible eye within 2 hours before any study visit.
7. Patient refusing to discontinue the use of contact lenses in the eligible eye during the study

7.3.2 Prohibited Concomitant Therapies

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

- Use of any artificial tears in the eligible eye other than those provided by the Sponsor.
- Use of topical CsA (i.e., RESTASIS ®), tacrolimus or sirolimus, in both eyes, and use of corticosteroids, antibiotics, pilocarpine, antihistamines, BAK preserved IOP lowering medications or any topical ocular treatments other than the study medication and BAK-free IOP lowering agents in the eligible eye.
- Contact lenses wear in the eligible eye during the study.
- Insertion of temporary punctal plugs in the eligible eye during the study.
- Implantation of diffractive multifocal intraocular lenses in the eligible eye.
- Any planned ocular laser/surgery in the eligible eye during the course of the study.
- Initiation or change in the dose of any of the following topical or systemic medications: Estrogen-progesterone or other estrogen derivatives (only for post-menopausal women), pilocarpine, isotretinoine, tetracycline, antihistamines, tricyclic antidepressants, anxiolytics, antimuscarinics, beta-blocking agents, phenothiazines, omega-3, systemic corticosteroids or other systemic immunosuppressant drugs

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

7.3.3 Recording of Medications

Any local or systemic treatment necessary for the patient's welfare has to be recorded on the Medication Form (product name, indication, treated eye, dose, route, frequency, start date and end date). Concomitant usage of artificial tears requires special attention, since this is considered a secondary endpoint. Patients will be allowed to use unpreserved artificial tears (only those provided by the Sponsor) up to eight instillations per day in the each eye, during the study period. Patients will be instructed not to use the unpreserved artificial tears within 30 minutes before or after use of the study medication and within two hours before a scheduled study visit.

The used/unused bottles of provided unpreserved artificial tears will be collected at each visit after the Screening Visit to record the concomitant usage of artificial tears during the study.

7.4 Criteria for Discontinuation or Withdrawal of a Patient

The primary reason for discontinuation or withdrawal of the patient from the study should be recorded in the case report form (eCRF) using the following categories. For screen failure patients, refer to Section 9.1.9.

1. Adverse event (AE). The patient has experienced 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.
2. Protocol deviation. The discovery after administration of the first dose of study drug that the patient failed to meet protocol entry criteria or 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 did not return to the clinic and attempts to contact the patient were unsuccessful. Attempts to contact the patient must be documented.
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, IRB, IEC, or regulatory agency terminates the study.
6. Lack of efficacy: the patient or the physician does not feel that the study medication has adequately relieved his/her 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 9.1.8.

8. Investigator decision due to non-compliance (to IMP, study visits or study related procedure)
9. Other reason, specify.

Note: All attempts should be made to determine the reason if Other (e.g. moving…).

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.4.1 Completed Study

The study enrolment will be considered as completed when the desired number of at least 33 included patients is reached. Patients completing the Wash-out Phase at the time the desired

number of 33 included patients is achieved are eligible for inclusion if they fulfil the inclusion/exclusion criteria at the Baseline Visits.

The 3-Month open-label study treatment period will be completed when all included patients complete the assessments of the Month 3 Visit in accordance with the study protocol.

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 the study termination criteria described in Section 7.3.2. In addition, a patient may discontinue his or her participation without giving a reason at any time during the study. Should a patient's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the Month 3/Early Termination (ET). Discontinued patients will not be replaced. Patients discontinued for AE(s) will be followed-up after patient's discontinuation until the event is resolved or considered medically stable by the investigator. In case of a patient lost-to-follow-up, the investigator must do his 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. The evidence of these contacts must be recorded in the patient medical chart.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Investigational Drug

IKERVIS® is a sterile, ophthalmic cationic oil-in-water emulsion containing 1 mg/ml CsA.

IKERVIS®, which was granted an European Marketing Authorization by the European Commission in 2015, contains the following excipients:

- Medium Chain Triglycerides (MCT): the emulsion's oily agent that constitutes the main droplet core component and solubilizes the drug.
- Cetalkonium chloride (CKC): a cationic surfactant that provides an efficient emulsification and a long-term stability by providing positive charges to the oil droplets which are stabilized by electrostatic repulsion. Positively-charged oily droplets are also electro-statically attracted to the membranes of the ocular surface epithelial cells that are negatively-charged.
- Tyloxapol (octyl phenol polyxyethylene) and poloxamer 188 (polyethylene oxide (PEO), polypropylene oxide (PPO) triblock copolymer): two non-ionic surfactants which ensure the emulsification by reducing the interfacial tension between the aqueous and the oily phases.
- Glycerol: a polyhydric alcohol used as tonicity agent in ophthalmic preparations. Glycerol is added in an appropriate quantity to adjust the osmolality of the emulsion.
- NaOH: used as a pH adjuster.
- Water: as diluents and the main emulsion component.

Batch number and expiration dates will be provided in the certificate of analysis.

8.1.1.2 Washout Medication

Unpreserved artificial tears will be provided to the patient during the wash-out phase to use as needed to ameliorate their symptoms of DED. Bottles of the unpreserved artificial tears (sodium chloride 0.9%, Larmabak®, Laboratoire Théa France) will be dispensed in the French commercial packaging.

8.1.1.3 Packaging and Labeling

IKERVIS® will be supplied in polyethylene single-dose containers presented in sealed laminate aluminum pouch package (1 pouch contains 5 single-dose containers).

- 8 aluminum pouches (i.e. 40 single-dose containers) of IKERVIS® will be placed together in a sealed cardboard box. One identical box will be dispensed for each of the three treatment phases: D0-M1 (Day 1 - Month 1), M1-M2 (Month 1 - Month 2) and M2-M3 (Month 2 - Month 3).

Each single dose container, aluminum pouch and sealed cardboard will carry an investigational label, indicating that the content is intended for investigational use only.

In addition, each cardboard box will carry a label bearing the protocol and treatment numbers.

8.1.2 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 medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day. The study medication and unpreserved artificial tears will be delivered to the study centres by the clinical supplies distributor. The study medication must be stored between 15 and 25°C. Initially each centre will receive adequate supplies (study medication 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 medication and unpreserved artificial tears during the course of the study.

8.1.3 Patient Identification

In order to ensure patient anonymity, patients will be identified by codes or other means of record identification, e.g.: 2 digits for site number, 2 digits for patient number by chronological order of entry in the study.

8.1.4 Dose and Regimen

During the 3-month study unpreserved artificial tears and the study medication must be dispensed only to study patients in accordance with the study protocol:

- At the Screening Visit each patient will be dispensed unpreserved artificial tears for use during the 2-week wash-out phase.

- At the Baseline Visit (on Day 1), after the validation of all inclusion and exclusion criteria, each eligible patient will be given unpreserved artificial tears and one sealed cardboard box containing enough study medication for the period Day 1 - Month 1.

- At Month 1 Visit, each patient will be given unpreserved artificial tears and one sealed cardboard box containing enough treatment for the period Month 1 - Month 2.

- At Month 2 Visit, each patient will be given unpreserved artificial tears and another sealed cardboard box containing enough treatment for the period Month 2 – Month 3.

At Screening Visit, each patient will be instructed to instil with unpreserved artificial tears up to eight times per day in each eye for the relief of their symptoms of DED, during the 3-month study treatment period. At the following visits, their compliance will be checked, and they will be instructed to pursue the use of unpreserved artificial tears according to their DED symptoms within the protocol limits.

At Baseline Visit (Day 1), each patient will be instructed to instil one drop of study medication (IKERVIS®, 1mg/ml ciclosporin) into the lower conjunctival sac of each eye once daily at bedtime during the 3-month study treatment period. Each single-unit container of study medication yields two drops of study medication (one drop for instillation in each eye) and will be used only once. At the following visits, their compliance will be checked, and they will be instructed to pursue the treatment with IKERVIS® with the same regimen.

Changes in the IKERVIS® regimen during the study are not permitted.

8.1.5 Accountability

The study medication and sponsor provided unpreserved artificial tears are to be dispensed only by the investigator or 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 medication have to be documented in the investigator's file provided by the Sponsor.

Patients will be instructed to keep all unused and used containers and will be required to bring study medication containers to each clinic visit, regardless of whether the study medication container is empty. The destruction of the used and unused containers of study medication 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 will, unless otherwise agreed, return to the clinical supplies distributor any surplus quantities, used and unused containers/bottles, of study medication or unpreserved artificial tears. The investigator will record each quantity of study medication or unpreserved artificial tears that has been damaged or is missing.

8.2 Patient's Compliance

Patient compliance will be assessed at each visit by the number of used and not used single-dose containers of study medication in relationship to the duration of the follow-up interval. All reported incidents of non-compliance and poor compliance will be recorded on the eCRF with the reasons. If a patient is persistently noncompliant with the study medication, the patient might be withdrawn from the study. All patients should be reinstructed about the dosing requirement during study visits. The authorized study personnel conducting the re-education must document the process in the patient source records.

8.3 Accountability and Destruction of All Study Medication

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

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to patients enrolled in the study. To document appropriate use of study drug, the investigator must maintain records of all study medication delivery to the site, site inventory, use by each patient, and return to the sponsor or designee.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labelled storage conditions, and is in good condition. See pharmacy manual for receipt of shipments. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and notifying Santen per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Santen must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must record the current inventory of all study medication on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of study medication, expiry and/or retest date, date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to who study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study

material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, patients are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A-I.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 14.1.

Informed consent must be obtained prior to the patient entering into the study, and before any protocol-directed procedures are performed.

A unique patient identification number will be assigned to each patient at the time that informed consent is obtained; this patient number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, alcohol and smoking status of the patient at Screening.

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

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 1 year prior to signing of informed consent.

9.1.3 Safety Assessments

On Day 1, all the assessments must be reviewed by the investigator prior to study treatment initiation to assure eligibility requirements have been met. During the study, all assessments should be done prior to administration of study drug unless otherwise indicated.

9.1.4 Wash-out Period

During the 2-week wash-out phase all enrolled patients must discontinue all prior DED therapies including artificial tears and any prohibited ocular treatments. The sponsor will provide all patients with unpreserved artificial tears to use up to eight instillations per day in each eye the relief of their symptoms of DED. Patients will be instructed in the optimal technique for ophthalmic drop instillation.

9.1.5 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the patient over the counter. Concomitant medication is not provided by Santen. At each study visit, patients will be asked whether they have taken any

medication other than the study medication (used from signing of informed consent through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.6 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (ie.,. diagnosis) should be described.

9.1.7 Contraception and Pregnancy Avoidance Procedure

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 Screening 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.

During the course of the study, urine hCG pregnancy tests will be performed only for women of childbearing potential and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the Schedule of Study Procedures **(Appendix A Schedule of Study Procedures and Procedures**

Appendix **-I).** Patients must have a negative urine pregnancy test on Day 1 and throughout the study.

9.1.8 Pregnancy

If any patient is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. If the pregnancy occurs during administration of active study medication, the pregnancy should be reported within 14 days of completing the study

All reported pregnancies in a patient receiving active study medication will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.9 Documentation of Screen Failure

Investigators must account for all patients who sign informed consent. If the patient is found to be not eligible at Screening or Baseline visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pre-treatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Major protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal, specify reason.
- Study termination.
- Other, specify reason.

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

9.1.10 Documentation of treatment initiation

Only patients who meet all of the inclusion criteria and none of the exclusion criteria are eligible for treatment initiation into the treatment phase.

If the patient is found to be not eligible for treatment initiation, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Patient Treatment Compliance

Study medication will be administered on Day 1, Month 2 and Month 3. The date and time of each dose will be recorded in the source documents and on the eCRF. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the patient's source document records or equivalent. If a patient is persistently noncompliant with the study medication, the patient might be withdrawn from the study. All patients should be reinstructed about the dosing requirement during study visits. The authorized study personnel conducting the re-education must document the process in the patient source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A-I. Assessments should be completed at the designated visit/time point(s).

The study period will include the initial Screening Visit, the 2-week wash-out phase, and the 3-month open-label study treatment phase encompassing the Baseline, Month 1, 2 and 3 study visits. See Appendix A for details of procedures that will be performed and documented.

9.3.1 Screening

Patients will be screened for the study within 14 days prior to the first dose of study medication. Patients will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.9 for procedures for documenting screening failures.

9.3.1.1 Screening Visit: Day -14 ± 3 days

Procedures to be completed at Screening Visit include:

- Informed consent.
- Inclusion/exclusion criteria review.
- Demographics.
- Ocular and systemic medical history.
- Previous and concomitant ocular and systemic medications (including artificial tear usage).
- Visual Analogue Scales (0-100%, from 0 = no symptom, 100 = maximal symptom) to assess the severity photophobia and blurred vision (Appendix A-II).
- Uncorrected distance visual acuity (UDVA).
- Best corrected distance visual acuity (BCDVA, Appendix A-III).
- Functional visual acuity parameters (FVA, starting visual acuity, LogMAR FVA, VMR, and maximal and minimal visual acuities) using FVA measurement system (AS-28; Kowa, Aichi, Japan / Nidek, Gamagori, Japan) (Appendix A-IV).

- Ocular Scatter Index (OSI), using double-pass aberrometer (Optical Quality Analyzing System, Visiometrics, Spain) (Appendix A-V).
- Root mean square (RMS) of higher order aberrations (total, coma-like, spherical like) using Hartmann-Shack aberrometer (Appendix A-VI).
- Slit lamp examination (Appendix A-VII).
- Tear break up time (TBUT).
- Corneal fluorescein staining (CFS, modified Oxford scale) (Appendix A-VIII).
- Eligible patients will discontinue all previous treatments related to dry eye including artificial tears and any prohibited ocular treatments.
- Urine pregnancy test (women of childbearing potential only)
- Dispense unpreserved artificial tears.
- Initiate 1-2 week wash-out phase.
- Patients will be scheduled to return to the clinic in 14 days $\pm$3 days for the baseline visit.

9.3.2 Treatment Phase

All assessments should be done in the mentioned order to ensure that additional product doesn't interfere for the other result examinations.

9.3.2.1 Baseline: Day 1

- Inclusion/exclusion criteria review.
- Record Ocular and systemic medical history.
- Review of concomitant ocular and systemic concomitant medications (including artificial tear usage).
- Record adverse events (AEs)
- 0-100% VAS for photophobia and blurred vision severity
- UDVA
- BCDVA
- FVA parameters using FVA measurement system
- OSI using double-pass aberrometry system
- Slit lamp examination
- Dilated fundus examination
- TBUT

- CFS (modified Oxford scale)
- IOP
- Schirmer test (without anaesthesia)
- Urine pregnancy test (women of childbearing potential only)
- Collection of unpreserved artificial tear bottles (used/not used)
- Verify inclusion and exclusion criteria based on evaluations just performed:
  - Patients **fulfilling** the inclusion / exclusion criteria will receive the study treatment for the next month
  - Patients **not fulfilling** the inclusion / exclusion criteria will be discontinued from the study and the patient become screen failure (refer to section 9.1.9)
- Dispense study medication and unpreserved artificial tears for a 1-month period. Patients will be instructed on dosing of study medication.
- Patients will be scheduled to return to the clinic in 28 days ± 3 days for Month 1 visit.

9.3.2.2 Month 1: Day 28 ±3 days

- Record concomitant ocular and systemic concomitant medications (including artificial tear usage)
- Record adverse events (AEs)
- 0-100% VAS for photophobia and blurred vision severity
- UDVA
- BCDVA
- FVA parameters using FVA measurement system
- OSI using double-pass aberrometry system
- Slit lamp examination

- TBUT
- Corneal fluorescein staining (modified Oxford scale)
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Dispense study medication and unpreserved artificial tears for a 1-month period (Month 1 - Month 2)
- Patients will be scheduled to return to the clinic on Day 56±3 days for Month 2 visit.

9.3.2.3 Month 2: Day 56 ±3 days

- Record concomitant ocular and systemic concomitant medications (including artificial tear usage)
- Record adverse events (AEs)
- 0-100% VAS for photophobia and blurred vision severity
- UDVA
- BCDVA
- FVA parameters using FVA measurement system
- OSI using double-pass aberrometry system
- Slit lamp examination
- TBUT
- Corneal fluorescein staining (modified Oxford scale)
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Dispense study medication and unpreserved artificial tears for a 1-month period (Month 2 - Month 3)
- Patients will be scheduled to return to the clinic on Day 84± 7 days for Month 3 visit.

9.3.2.4 Month 3: Day 84 ±7 days

- Record concomitant ocular and systemic concomitant medications (including artificial tear usage)
- Record adverse events (AEs)
- Patient global evaluation of efficacy
- 0-100% VAS for photophobia and blurred vision severity
- UDVA
- BCDVA
- FVA parameters using FVA measurement system
- OSI using double-pass aberrometry system
- RMS of higher order aberrations using Hartmann-Shack aberrometer
- Slit lamp examination
- Dilated fundus examination

- TBUT
- CFS including assessment of complete corneal clearing (modified Oxford scale)
- IOP
- Schirmer test (without anaesthesia)
- Investigator global evaluation of efficacy
- Urine pregnancy test (women of childbearing potential only)
- Collection of study medication containers used/not used study medication containers and unpreserved artificial tear bottles.

9.3.3 Unscheduled Visit/Premature Discontinuation

An unscheduled visit may be performed as needed between two scheduled visits. The reason for the visit will be recorded on the eCRF. The examinations required at an unscheduled visit will be at the discretion of the investigator.

If necessary, (e.g. to follow up an AE), the investigator may schedule further "unscheduled" visits at his/her discretion. Data from an unscheduled visit will not be collected in the eCRF with the exception of information related to an AE or the follow-up of an AE.

In case of premature study discontinuation between two scheduled visits, the Unscheduled Visit Form and the Exit Forms will be completed. If the premature discontinuation occurs during an Unscheduled Visit prior to Month 3, the investigator will complete and record all of the exams scheduled at the Month 3 Visit on the Unscheduled Visit Form. In case of premature study discontinuation, the investigator will ensure that all used and unused study medication for the study period has been collected from the patient.

9.3.4 Efficacy Assessment

9.3.4.1 Functional Visual Acuity (FVA)

Functional visual acuity (FVA) will be measured without topical anaesthesia using FVA measurement system (AS-28; Kowa, Aichi, Japan) at each study visit (see Appendix A-I). The FVA is defined as the mean value of time-wise change of the visual acuity during the overall examination (60 seconds). The LogMAR FVA, starting VA, and maximal and minimal VAs will also be determined.

The visual maintenance ratio (VMR) which is the primary efficacy criteria will be calculated: it is defined as the ratio of FVA divided by the value of starting VA (Kaido 2006, Kaido 2011)

An increase in VMR from baseline will indicate improvement.

9.3.4.2 Objective Scatter Index (OSI)

Ocular Scatter Index (OSI) and its variance will be measured using double-pass aberrometer (Optical Quality Analyzing System, Visiometrics, Spain) at each study visit (see Appendix A-V).

A decrease in OSI variance from baseline will indicate improvement.

9.3.4.3 Corneal Fluorescein Staining including Complete Corneal Clearing

Corneal 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. The eye 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 (see Appendix A-VIII). On this modified scale, the score 0 corresponds to no staining dots and the score 0.5 to three or less staining dots. A CFS grade of 0 represents complete corneal clearing.

A negative change from baseline will indicate improvement.

9.3.4.4 Higher Order Aberrations

Root mean square (RMS) of higher order aberrations (total, coma-like, spherical like) will be measured using Hartmann-Shack aberrometer (see Appendix VI).

A decrease in RMS from baseline will indicate improvement.

9.3.4.5 Patient Global Evaluation of Efficacy

Patient will conduct an overall assessment of the effect of the study medication using the following rating scale:

(3) = Very satisfactory.

(2) = Satisfactory.

(1) = Not very satisfactory.

(0) = Unsatisfactory.

9.3.4.6 Symptoms Measured on Visual Analogue Scales (VASs)

Patient's photophobia and blurred vision will be assessed using a self-administered VASs ranging from 0% to 100% (see Appendix A-II).

A decrease in the VAS % from baseline will indicate improvement.

9.3.4.7 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 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. This measurement will be performed within 10 seconds maximum. 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 a then a third reading is taken.

The TBUT value will be the average of the 2 or 3 measurements. A measured value of less than 10 seconds will be recorded or 10 seconds will be indicated.

A positive change from baseline will indicate improvement.

9.3.4.8 Schirmer Test (without anesthesia) (mm wetting/5min)

Schirmer 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 directly the Schirmer test strip with the fingers to avoid contamination of skin oils. After 5 minutes have elapsed the Schirmer test strip is removed and the length of the tear absorption on the strip will be measured.

A positive change from baseline will indicate improvement.

9.3.4.9 Use of Concomitant Artificial Tears

The use of artificial tears will be monitored over the course of the study for each patient. Patients will be asked about the average number of times per day artificial tears was used the week preceding the visits, and number of days they were not used during the week preceding the visits

The Sponsor will provide unpreserved artificial tears for all the patients. After the Screening Visit patients will be allowed to instil 1 unpreserved artificial tear drop, up to eight instillations per day in each eye, to ameliorate their dry eye symptoms. Patients will be instructed not to use the unpreserved artificial tears within 30 minutes before or after the use of the study medication. Patients will also be instructed not to use the unpreserved artificial tears two hours before the scheduled study visit.

Patients will be instructed to return the used or not used unpreserved artificial tears at the scheduled study visits.

9.3.4.10 Investigator Global Evaluation of Efficacy

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

(3) = Very satisfactory.

(2) = Satisfactory.

(1) = Not very satisfactory.

(0) = Unsatisfactory.

9.3.5 Safety Evaluation Parameters

9.3.5.1 Slit lamp examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp. The subject 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-VIII.

9.3.5.2 Uncorrected Distance Visual Acuity (UDVA)

The uncorrected distance VA will be measured in LogMAR.

9.3.5.3 Best Corrected Distance Visual Acuity (BCDVA)

Best corrected distance VA will be measured with the patient's best correction and recorded in LogMAR (see Appendix A-III).

9.3.5.4 Dilated Fundus Examination

A dilated fundus examination will be performed after use of mydriatic eye drops to dilate the pupil in order to evaluate for posterior segment diseases. Abnormal outcomes will be described.

9.3.5.5 Tonometry for measurement of Intraocular Pressure (IOP) (mmHg)

IOP will be measured using Goldman applanation tonometry (one measurement), after instillation of one drop of oxybuprocaine 0.4% and fluorescein 0.5% solutions. 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 test especially). The patient and slit lamp should be adjusted so that the patient's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Both eyes will be tested, with the right eye preceding the left eye. The same equipment must be used throughout the course of the study. All equipment (i.e., slit lamp) should be calibrated and checked during monitoring visit.

9.3.5.6 Ocular Adverse Events (AEs)

Ocular AEs will be recorded in the eCRFs as described in Section 5.6. Any clinically significant change in ocular concomitant disease or any new concomitant ocular conditions that occurred between the Screening Visit and the Baseline Visit will be reported as AEs.

9.3.5.7 Systemic Adverse Events (AEs)

Systemic AEs will be recorded in the eCRF as described in Section 5.6. Any clinically significant change in concomitant disease or new concomitant conditions that occurred between the Screening Visit and the Baseline Visit will be reported as AEs.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pre-treatment Events

A pre-treatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation patient who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in patient or clinical investigation patient administered an investigational product; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not it is considered related to the drug.

10.1.3 Sight-threatening Events

An event is considered sight-threatening and should be reported as an SAE if it meets one or more of the following criteria:

- It caused a decrease in visual acuity of >30 letters (compared with the last assessment of visual acuity at the last visit) lasting >1 hour
- It caused a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour
- It required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis)
- In the opinion of the investigator it may require medical intervention to prevent permanent loss of sight

10.1.4 Case of Special Interest

The following cases are considered to be of special interest by the sponsor:

- Overdose:

  Administration of a quantity of a medicinal product exceeding the dose defined in the study protocol/otherwise specify overdose.

- Misuse of study product:

  Situations where the medicinal product is intentionally and inappropriately used not in accordance with the study protocol.

- Medication error:

  Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

- Abuse of study product:

  Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

10.1.5 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavourable by the investigator for any reason.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values:

- Changes in laboratory values are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional non-invasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a patient has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a patient has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the patient experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the patient experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the patient experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Pre-planned surgeries or procedures:

- Pre-planned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a pre-planned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as adverse events.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the patient's medical condition should not be recorded as PTEs or AEs, but should be documented in the patient's source documents. Complications resulting from an elective surgery should be reported as adverse events.

Overdose, medication error, abuse or misuse:

- Cases of overdose, medication error, abuse or misuse with any medication without manifested side effects are NOT considered PTEs or AEs, however, theywill be documented on the AE page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded separately on the AE page of the eCRF.

10.1.6 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the patient to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

PTEs that fulfil 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.1).

10.1.7 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the patient.
Moderate:	The event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The event causes considerable interference with the patient's usual activities.

10.1.8 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.9 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as "Related" if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as "Not related".

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the patient signs the informed consent to participate in the study and continue until the patient is first administered study medication or until screen failure. For patients who discontinue prior to study medication administration, PTEs are collected until the patient discontinues study participation.

Collection of AEs will commence from the time that the patient is first administered study medication. Routine collection of AEs will continue until the Final Visit.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Patients may report AEs occurring at any other time during the study. Patients experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory

values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or not related to the study procedure, need not to be followed-up for the purposes of the protocol.

All patients experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date and time.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (Related or Not related) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Santen SAE form must be completed, in English, and signed by the investigator immediately but not later than within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Patient identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted immediately but not later than within 24 hours to the attention of

Santen EMEA, Pharmacovigilance Unit (PVU)

Fax SAE Report Form to: Fax: +358 3 318 1060 or

Email to: SafetyEU@santen.com

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately but not later than within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, post-mortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted without any delay for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary, based upon Anatomical-Therapeutic-Chemical (ATC) system.

11.1 Electronic eCRFs

Completed eCRFs are required for each patient who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Santen personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs s for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the database lock of clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign, and date the form.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

11.2 Source Data Documentation

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 (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 AE and/or SAEs occurred during the time course of the study an within one month after last treatment received
- Any data that could be judged by the Investigator as relevant

11.3 **Record Retention**

The investigator agrees to keep the records stipulated in Section 11.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, patient authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. 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 Site Agreement between the investigator and sponsor.

12.0 STATISTICAL METHODS

12.1 Statistical Analysis

Descriptive statistics (mean, standard deviation, 95% confidence interval for mean, minimum, median, maximum, and number of observations and missing cases) will be used for quantitative variables, and frequencies and percentages will be used for categorical variables. For the variables recorded for both eyes, the descriptions will be given separately for the analysis eye and for the fellow eye, when considered relevant.

All the efficacy analysis will be performed on the analysis eye, which is defined as the eligible eye that fulfils all the criteria listed under the inclusion criteria #4. If both eyes are eligible, the eye with the highest baseline CFS score will be chosen. If both eyes have the same CFS score, the eye with the lowest VMR will be chosen. If VMR values are the same for both eyes, the right eye will be chosen.

A Statistical Analysis Plan will be written and signed before starting the analysis of the study data. This document will present all the analyses to be performed, and detail some points of the protocol.

12.2 Analysis of Demographics and Other Baseline Characteristics

Baseline patient characteristics (demographics, ocular history, clinical examination etc.) will be summarized using descriptive statistics.

12.3 Primary Efficacy Variable Analysis

Spearman's coefficient of correlation will be calculated at Month 3 between the change from baseline of CFS and respectively the change from baseline of VRM and the change from baseline of variance of OSI.

As a sensitivity analysis, a mixed effects model will also be employed to investigate the association between the change in CFS vs. change in VMR, and change in CFS vs. change in variance of OSI, respectively, during the course of the study (from baseline to Month 3).

Changes from baseline in VMR and variance of OSI will also be summarized by categorical change in CFS (-5, -4.5, -4, -3.5, -3, -2.5, -2, -1.5, -1, 0, +1 unit change) and by analysis visit (Month 1, Month 2, and Month 3).

12.4 Analysis of the Secondary Efficacy Variables

Spearman's coefficients of correlation will be calculated at each time-point (M1, M2, M3) between the change from baseline of CFS and respectively the change from baseline of other FVA parameters (starting visual acuity, FVA, LogMAR FVA), and maximal and minimal visual acuities) and the change from baseline of OSI parameters.

Spearman's coefficients of correlation will be also calculated at each time-point (M1, M2, M3) between the change from baseline of OSI and of variance of OSI separately and the change from baseline of each FVA parameters.

The graphical curve (with means and error bars at each visit) of each parameter (CFS score, FVA parameters, OSI, variance of OSI) will be generated to explore their pattern of evolution over time (from baseline to Month 3) under the IKERVIS® treatment.

The other efficacy endpoints will be presented with descriptive statistics at each time-point and in term of change from baseline. The coefficient of variation will be calculated for each criterion in order to provide reliable information on their metric interest for a further study.

12.5 Safety Assessments

Other parameters of safety or tolerance (e.g. slit lamp examination, visual acuity, IOP) will be described at each time point of measurement, and they will be summarized/ analysed for both the analysis eye and the fellow eye separately.

12.6 AEs

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages will be provided of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation. An adverse event is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of patients with TEAEs as follows: 1) by system organ class, by system organ class and preferred term, 2) by system organ class, preferred term and maximal severity, 3) by system organ class, preferred term and strongest relationship, and 4) by system organ class, preferred term, maximal severity, and strongest relationship.

Separate analyses will be performed for ocular and systemic adverse events. Ocular AEs will be summarised for the analysis eye and the other eye separately.

12.7 Interim Analysis

No interim analysis is planned.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action.

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign countries. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the summary of product characteristics, the patient information leaflet, a copy of the informed consent form, and, if applicable, patient recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will [ship drug/notify site] once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received written permission from competent authority to begin the trial. Until the site receives [drug/notification] no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

14.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations (Appendix B). The informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and

permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the patient authorization form. The informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the patient, or the patient's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and prior to the patient entering into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and patient authorization (if applicable) at the time of consent and prior to patient entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed informed consent form, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised informed consent forms must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised informed consent form.

14.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will only be linked to the sponsor's (or designee) clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, External Study Coordinator under Confidentiality Agreement, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., patient name, address, and other identifier fields not collected on the patient's eCRF).

All information from this study (excluding data from the informed consent) are entered into a computer under the sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978 and subsequent amendments) and with the European Directive 95/46/EC.

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

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. 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.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Santen will, at a minimum, register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation.

14.4.3 Clinical Trial Results Disclosure

Santen will minimally post the results of clinical trials conducted in patients, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Master Services Agreement or equivalent agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures and Procedures

Appendix A-I Schedule of Study Procedures

Study procedures	Wash out period	Open-label study treatment Period				Unscheduled Visit / premature study discontinuation
	Screening Day –14 ± 3	**Baseline** Day 1	**Month 1** Day 28 ± 3	**Month 2** Day 56 ± 3	**Month 3** Day 84 ± 7	
Informed consent	X					
Demographic information	X					
Ocular and systemic medical history	X	X				
Previous and Concomitant ocular and systemic medications (incl. concomitant artificial tear usage)	X	X	X	X	X	X[4]
Inclusion/exclusion criteria	X	X				
Efficacy Assessments						
Tear break up time (TBUT)	X	X	X	X	X	X[4]
Corneal fluorescein staining (Modified Oxford Scale)	X	X	X	X	X	X[4]
Schirmer test (without anaesthesia)		X			X	X[4]
Functional visual acuity (FVA parameters, FVA system)	X	X	X	X	X	X[4]
Objective scatter index (OSI) (double-pass aberrometer)	X	X	X	X	X	X[4]
RMS/Higher-order aberrations (Hartmann-Schack aberrometer)	X				X	X[4]
Investigator global evaluation					X	X[4]

Study procedures	**Wash out period**	**Open-label study treatment Period**				**Unscheduled Visit / premature study discontinuation**
	Screening Day –14 ± 3	**Baseline** Day 1	**Month 1** Day 28 ± 3	**Month 2** Day 56 ± 3	**Month 3** Day 84 ± 7	
Patient global evaluation					X	X[4]
Visual Analog Scale (VAS) (photophobia, blurred vision)	X[1]	X[1]	X[1]	X[1]	X[1]	X[1,4]
Safety Evaluations						
Slit lamp examination	X	X	X	X	X	X[4]
Uncorrected distance visual acuity (UDVA in LogMAR)	X	X	X	X	X	X[4]
Best corrected distance visual acuity (BCDVA in LogMAR)	X	X	X	X	X	X[4]
Dilated fundus examination		X			X	X[4]
Intraocular Pressure (IOP)		X			X	X[4]
Urine pregnancy test (women of childbearing potential only)	X	X[3]			X	X[5]
Confirm patient discontinued treatment related to dry eye	X					
Adverse events (AEs)		X	X	X	X	X[4]
Treatment Procedures						
Dispense study medication and unpreserved artificial tears	X[2]	X[2]	X[2]	X[2]		
Collection of used study medication and unpreserved artificial tears		X	X	X	X	X[4]

Footnotes are on last table page.
ET/EOT=early termination/end of treatment.
1 VASs should be performed at the beginning of the visit before medical history and any study assessment see visit schedule section 9.3.
2 Dispense unpreserved artificial tears. Instruction: to be instilled up to eight times per day in each eye
3 Only for patients fulfilling criteria for severe keratitis that will be included.
4 Assessments to be performed during unscheduled visits only in case of premature discontinuation

Appendix A-II 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 2 symptoms, i.e., blurred vision and photophobia. The patient will be asked to rate each ocular symptom of each eye by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort."

Blurred Vision	0%	50%	100%
	|_____|		
Photophobia	0%	50%	100%
	|_____|		

The response will be measured in % between 0 – 100%.

Appendix A-III Best Corrected Distance Visual Acuity Procedure in LogMAR

The distance visual acuity test should be done with the best correction. The investigator will use the same chart for both eyes throughout the study.

Equipment:

An ETDRS or modified ETDRS chart may be used.

If a Lighthouse chart is used (dimensions 62 x 65 cm / 24.5 x 25.5 inches), the patient must be seated at 4 meters (13 feet) from the chart. If a smaller reproduction is used (dimensions 45.5 x 45.5 cm / 18 x 18 inches), the patient must be seated at 3 meters (10 feet) from the chart.

The same lighting conditions must be used throughout the course of the study.

Procedure:

The patient should be seated in front of the chart.

The right eye must be tested first and the left eye must be covered. The patient should try to read each letter, from left to right, beginning at the top of the chart. The patient must be told that the chart contain only letters and no numbers. The patient must read slowly (about one letter per second). The investigator should not point on the chart during the test, but he must push /motivate the patient to read as far as he can during the test. The test is stopped when the patient cannot read any correct letter on the chart with the right eye.

During the test, the investigator must count all the missed letters (=errors):

- If the patient changes his response after reading the next letter, the change is regarded as an error.
- If the patient cannot read one letter, this is regarded as an error too.

Please note that if the patient changes his response before reading the next letter, this change is not regarded as an error.

The same procedure must be repeated with the left eye.

LogMAR calculation:

The investigator must calculate the score as follows:

LogMAR Visual acuity = baseline value + (N x 0.02)

With:

- Baseline value: this is the lowest line where the patient can read at least one correct letter
- N: this is the total number of missed letters (letters read incorrectly or letters not read up to the last/baseline line)
- 0.02 is the value for each letter

Example:

If a patient misses 3 letters of 5 at the 0.2 LogMAR line and 4 letters of 5 at the line 0.1 (lowest line where the patient can read at least one correct letter), the calculation is:

- Last line read = 0.1 = baseline value
- N = 4+3 = 7

Then score = 0.1 + (7 x 0.02) = 0.24 LogMAR

If a patient misses 2 letters of 5 at the 0.0 LogMAR line and 3 letters of 5 at the line -0.1 (lowest line where the patient can read at least one correct letter), the calculation is:

- Last line read = -0.1 = baseline value
- N = 2+3 = 5

Then score = -0.1 + (5 x0.02) = 0.0 LogMAR

Appendix A-IV Functional Visual Acuity (Kaido 2013).

The functional visual acuity (FVA) will be measured using FVA measurement system (AS-28; Kowa, Aichi, Japan) at each study visit. The changes with time in the continuous visual acuity using the Landolt optotypes (Figure 2) with their sizes change depending on the correctness of the responses.

The optotypes are displayed automatically, starting with smaller ones. When the response is correct, even smaller optotypes are presented. If the responses are incorrect, larger optotypes are presented automatically (Figure 3). Visual acuity is continuously measured from the baseline best corrected Landolt visual acuity. The functional visual acuity measurement system can measure visual acuity from 150/100 to 20/200. When there is no response within the set display time, the answer is assumed to be an error, and the optotype enlarged automatically.

The outcomes will be recorded as starting visual acuity, LogMAR functional visual acuity, visual maintenance ratio, and maximal and minimal visual acuities:

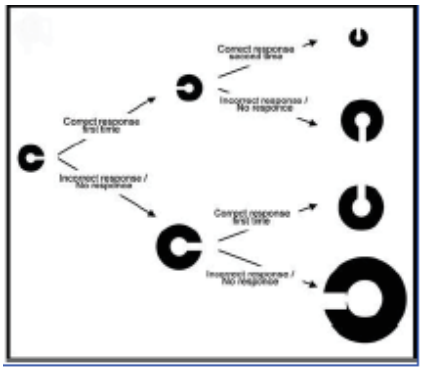
- Starting visual acuity is defined as the baseline visual acuity, which is the value of the standard best corrected visual acuity measured by the functional visual acuity measurement system
- Functional visual acuity is defined as the mean value of time-wise change of the visual acuity during the overall examination
- Visual maintenance ratio (VRM) is calculated as follows (Kaido 2006, Kaido 2011):

  visual maintenance ratio = (lowest LogMAR visual acuity score –functional visual acuity at 60 s)/(lowest LogMAR visual acuity score – baseline visual acuity)

  An increase in VMR from baseline will indicate an improvement.
- Maximal and minimal visual acuities are defined as the highest and lowest visual acuities recorded during the examination.

Figure 2 Presentation of Landolt optotypes on mini-pointer of the functional visual acuity device (Kaido 2013).

Figure 3 flowchart diagram of optotypes during functional visual acuity testing (Kaido 2013).



Appendix A-V Objective Scatter Index (Habay et al 2014)

Objective Scatter Index (OSI) and its variance will be measured using double-pass aberrometer at each study visit.

The system is driven by a software allowing a dynamic measure of the Point Spread Function (PSF) over 20 seconds with a resolution of half a second. For each PSF measure, the OSI is calculated, corresponding to the ratio of the light recorded in a ring area of 12 to 20 minutes of arc, and a circular area of 1 minute of arc.

Before proceeding to the test, the patient closes his/her eyes for 10 sec, then blinks 5 times to obtain the most homogenous spreading of the lachrymal film on the cornea surface.

Each measure is to be performed once. When measurement is to be performed on both eyes in the same patients, results will be considered as independent.

A decrease in OSI variance from baseline will indicate improvement.

Appendix A-VI Higher Order Aberrations

Serial measurements of ocular higher-order aberrations are performed by means of Hartmann-Shack wavefront aberrometer.

Higher-order aberrations will be measured during a blink-free period of 20 seconds without instillation of topical anesthesia.

The higher-order aberration data will be analysed quantitatively for the central 4-mm-diameter zone up to the fourth order by expanding the set of Zernike polynomials. From the Zernike coefficients, the root mean square (RMS) will be calculated to represent the wavefront aberrations. The third-order Zernike coefficients (coma-like aberrations, S3), fourth-order Zernike coefficients (spherical-like aberrations, S4), and total higher-order aberrations (S3 + S4) will be calculated.

Appendix A-VII Slit lamp examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp. The subject 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 localized 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 (localized 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 localized swelling).
2 = Moderate (moderate/medium localized 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 (Slit beam= 0.3 mm wide, 1.0 mm long)

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).

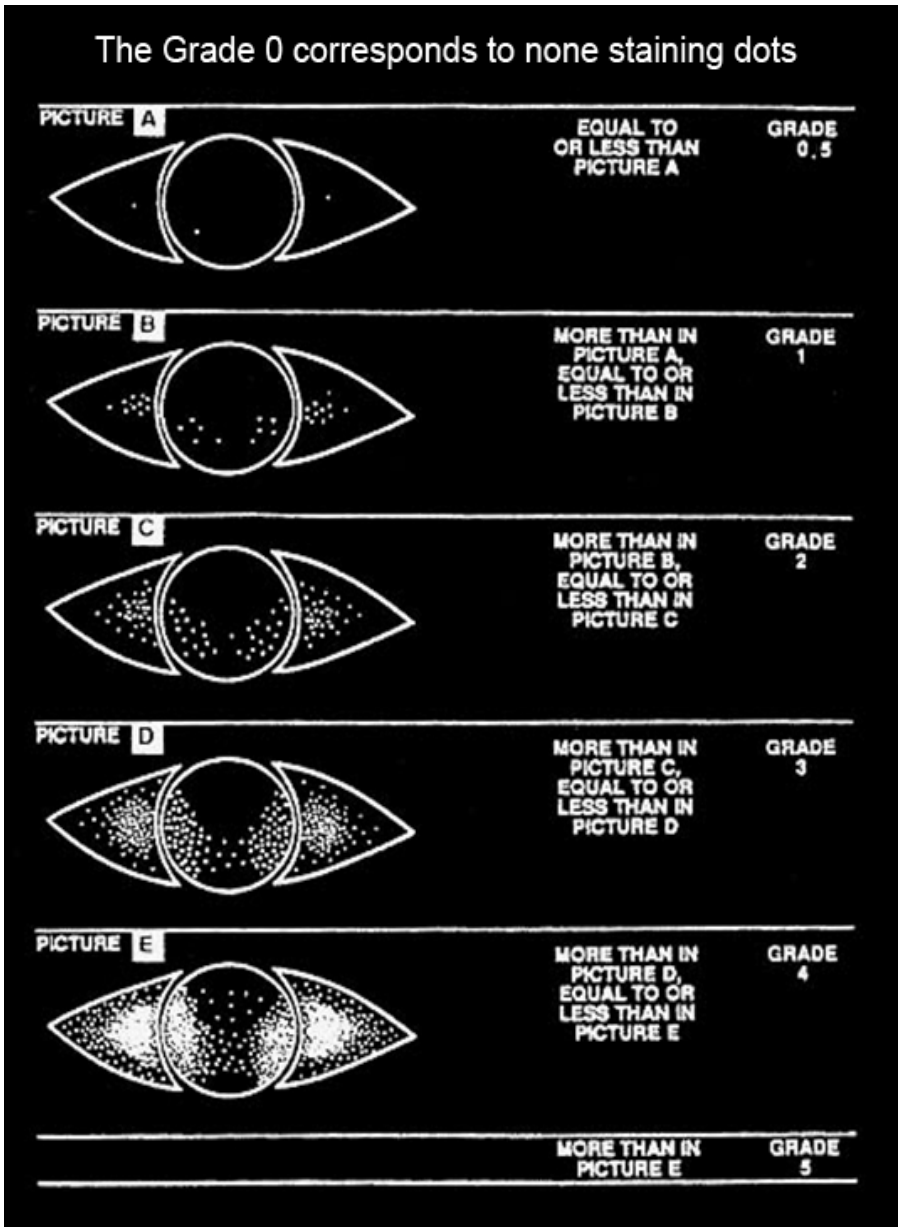
Lens

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

Vitreous

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

Appendix A-VIII Modified Oxford Scale



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, fetus, 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.
- A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
- 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 subject's willingness to continue participation, will be provided to the subject.
- 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 medication(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.

1. Female patients of childbearing potential (e.g., non-sterilized, premenopausal female patients) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening through 90 days after the last dose of trial treatment. Regular pregnancy tests will be performed throughout the study for all female patients of childbearing potential. If a patient is found to be pregnant during study, study medication will be discontinued.
2. Male patients must use adequate contraception (as defined in the informed consent) from Screening through 90 days after the last dose of trial treatment.

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 medication.
- 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.

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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and this page is the manifestation of the electronic signature.