Study Protocol Cover Page

Official Study Title:	A Phase IIIb, Prospective, Interventional, Multicentre, 3-year Study to Explore the Long-term Evolution of Sign and Symptoms, and Occurence of Complications in Dry Eye Patients With Severe Keratitis Receiving Ikervis® (1mg/mL Ciclosporin)
NCT Number:	NCT04144413
Date of the document:	17 October 2018

PROTOCOL NVG14L127

A PHASE IIIb, PROSPECTIVE, INTERVENTIONAL, MULTICENTRE, THREE-YEAR STUDY TO EXPLORE THE LONG-TERM EVOLUTION OF SIGN AND SYMPTOMS, AND OCCURRENCE OF COMPLICATIONS IN DRY EYE DISEASE PATIENTS WITH SEVERE KERATITIS RECEIVING IKERVIS® (1MG/ML CICLOSPORIN) EYE DROPS

Sponsor:	SANTEN SAS Genavenir IV, 1 rue Pierre Fontaine F-91058 Evry, France		
Study Number:	NVG14L127		
IND Number:	N/A	**EudraCT Number:**	2017-002660-41
Compound:	IKERVIS® (1mg/mL Ciclosporin)		
Date:	Version 3.0 17 October 2018 Amendment 1		

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 12.2.4.3 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I confirm my responsibilities noted on Appendix B of this Protocol.

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

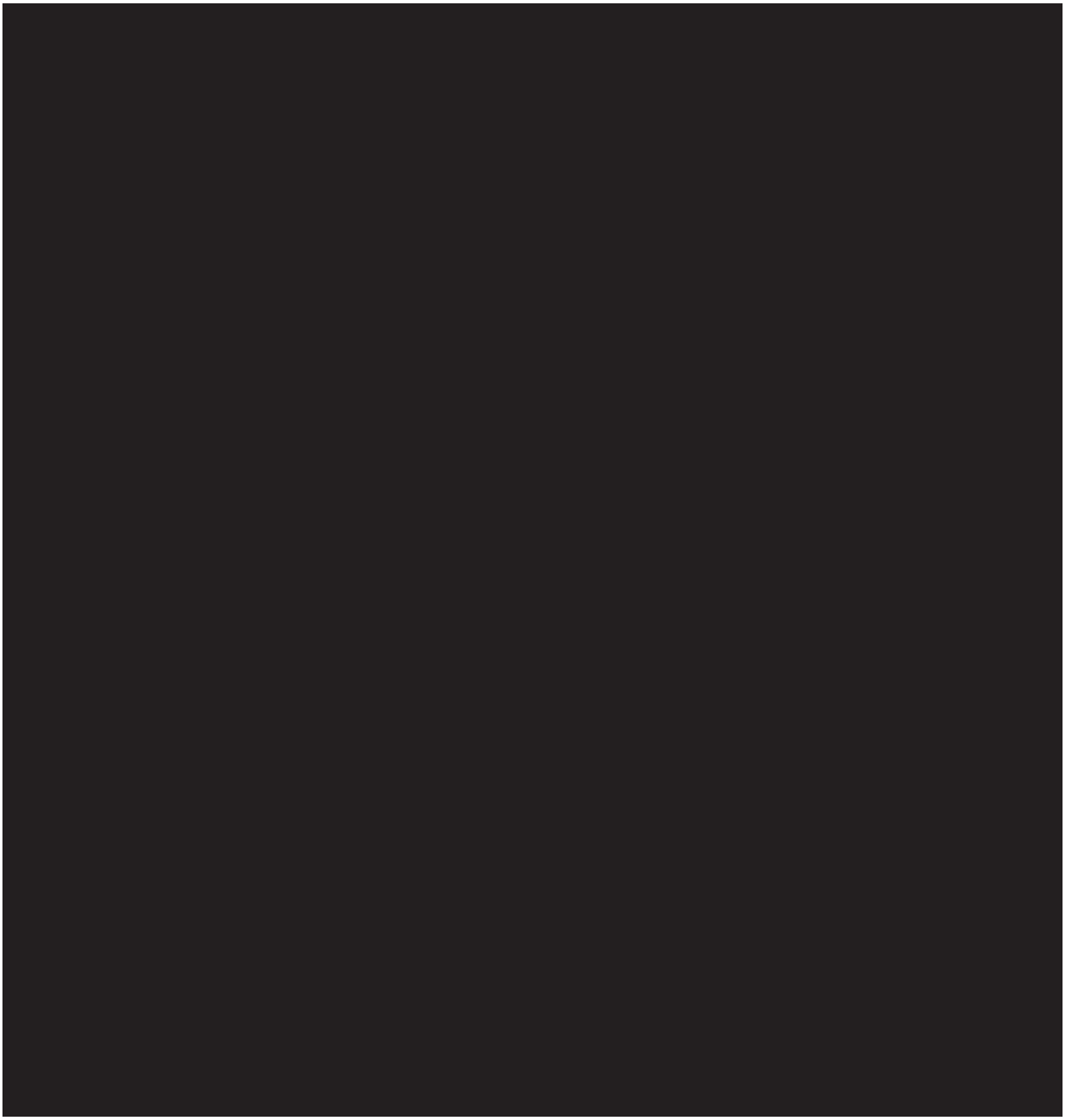
_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State)

_____
Location of Facility (Country)

_____
Signature of Investigator Date



1. SYNOPSIS

Name of Sponsor/Company: SANTEN SAS, France	
Name of Active Ingredient: Ciclosporin	
Title of Study: A Phase IIIb, prospective, interventional, multicentre, three-year study to explore the long-term evolution of sign and symptoms, and occurrence of complications in Dry Eye Disease patients with severe keratitis receiving IKERVIS® (1mg/ml ciclosporin) eye drops	
Coordinating Investigators: [redacted]	
Studied period (years): Estimated date first patient enrolled: February 2019 Estimated date last patient completed: February 2023	**Phase of development:** IIIb
Objectives: **Primary:** • To evaluate the long-term efficacy of a continuous treatment of IKERVIS® (1mg/mL ciclosporin) eye drops in adult dry eye disease (DED) patients with severe keratitis on corneal sign and DED symptoms, and to estimate the lag time (if any) to improvement in symptoms (if any). • To assess the ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity, and ocular infection) over the three-year study period. **Secondary:** • To evaluate the efficacy parameters (signs and symptoms), the ocular surface complications, and the quality of life over treatment Periods 1 and 2. • For 12-month markedly improved patients, to evaluate and compare signs and symptoms evolution in IKERVIS® group versus Vehicle group during the randomised period of the study (Period 2). • To evaluate the safety and tolerability of IKERVIS® (1mg/mL ciclosporin) eye drops treatment over the three-year study period.	
Methodology: Phase IIIb, prospective, interventional, multicentre study. Duration of the study: All enrolled patients will enter a period of 12 months of treatment (Period 1) and attend 5	

visits:

- Period 1 (12-month open-label IKERVIS® treatment period): Baseline visit (Day 1), Month 3, Month 6, Month 9 and Month 12
- At Month 12 visit, markedly improved patients will continue the study during 24 additional months until Month 36 (Period 2) and will be randomised to receive IKERVIS® or vehicle (using a ratio of 3:2) in a double-masked fashion; the patients will attend 8 visits: Period 2 (Double-masked randomised period IKERVIS® or vehicle treatment for markedly improved partients at Month 12): Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, and Month 33 visits and Final visit Month 36

Markedly improved patients are defined as patients having a corneal fluorescein staining (CFS) score improvement from baseline of 2 grades or more on the modified Oxford scale [unless if the patient had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more] in the analysis eye.

Patients who will not be markedly improved at Month 12 (cf. definition above) will be early terminated from the study.

Number of patients (planned): 350 DED adult patients with severe keratitis having CFS grade 3 or above on the modified Oxford scale and with at least half of them having a CFS grade 4 or 5.

It is expected that almost 70% of the included patients (approximately 245 patients) would enter the Period 2 (Double-masked randomised period) after Month 12.

This study will be conducted in about 52 trial sites.

Diagnosis and main criteria for inclusion:

Patient eligibility is determined according to the following inclusion criteria:

1. In the opinion of the investigator, the patient is capable of understanding and complying with protocol requirements.
2. The patient has signed and dated 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. At least 4 weeks of use of tear substitutes prior to the Baseline Visit.
5. DED patients with severe keratitis defined as the following:
    - CFS score of 3, 4 or 5 on the modified Oxford scale in at least one eye at Baseline Visit

    AND

    - Schirmer test without anaesthesia scored < 10 mm/5min in the same eye at Baseline Visit,

    AND

- At least two moderate to very severe symptoms of dry eye disease with a score ≥2 (severity graded on a 0 to 4 grade scale), among the following symptoms: burning/stinging, foreign body sensation, eye dryness, eye pain and blurred/poor vision at Baseline Visit.

6. Patient must be willing and able to undergo and return for scheduled study-related examinations.

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

1. Active herpes keratitis or history of ocular herpes.
2. History of ocular trauma or ocular infection (viral, bacterial, fungal, protozoal) within 90 days before the Baseline Visit.
3. Any ocular diseases other than DED requiring topical ocular treatment during the course of the study. Patients taking preservative-free IOP lowering medications are eligible for study enrolment.
4. Concurrent ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye.
5. Anticipated use of temporary punctal plugs during the study. Patients with punctal plugs placed prior to the Baseline Visit are eligible for enrolment; however, punctal plugs must remain in place during the study.
6. Best corrected distance visual acuity (BCDVA) score ≤ 20/200 Snellen in each eye.
7. 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 or judged by the investigator to be incompatible with the study (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections, ocular infection…).
8. Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein, etc...).
9. History of ophthalmic malignancy.
10. History of malignancy (other than ophthalmic) in the last 5 years
11. 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.
12. Use of topical ciclosporin in the past 3 months prior to Baseline visit.

13. Any change in systemic immunosuppressant drugs within 30 days before the Baseline Visit or anticipated change during the course of the study.
14. Pregnancy or lactation at the Baseline Visit.
15. Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomised partner) from the Baseline Visit throughout the conduct of the study treatment periods and up to 2 weeks after the study end. Post-menopausal women (two years without menstruation) do not need to use any method of birth control.
16. Participation in a clinical trial with an investigational substance within the past 30 days prior to Baseline Visit.
17. Participation in another clinical study at the same time as the present study.

Investigational product, dosage and mode of administration:

Investigational product: IKERVIS® (1 mg/ml ciclosporin) eye drops single-dose containers.

Investigational product dose: 1mg/ml ciclosporin (CsA)

Regimen: Instillation of one drop in each affected eye, once daily at bedtime.

Duration of treatment:

The duration of treatment is up to 36 months except for non markedly improved patients at Month 12 for whom the duration of treatment is up to 12 months.

Reference therapy, dosage and mode of administration:

Reference Product (for markedly improved patients at Month 12 to use in Period 2): Vehicle of IKERVIS® - sterile, ophthalmic cationic oil-in-water emulsion containing no active substance.

Regimen: Instillation of one drop in each affected eye, once daily at bedtime.

Criteria for evaluation:

Efficacy:

Efficacy will be assessed by evaluating CFS score, symptoms score ("Symptom Assessment iN Dry Eye" [SANDE] questionnaire and 5-point scale), correlation between sign and symptoms, conjunctival fluorescein staining score, TBUT, Schimer test, use of artificial tears, and quality of life.

Safety:

Safety assessments will be composed of ocular surface complications, adverse events, Intraocular Pressure (IOP), and Best Corrected Distance Visaul Acuity (BCDVA)

Endpoints:

Primary Efficacy and Safety Endpoints:

- The correlation between mean change from baseline in CFS score and SANDE symptoms score at each visit, and cross correlation of sign at visit X versus symptoms at visit X+i (i starting from 0), if any.
- Incident rate and time to onset of ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity and ocular infection)

Secondary Endpoints:

Efficacy:

A) In Period 1:

- CFS score and change from baseline at each visit
- Conjunctival fluorescein staining score and change from baseline at each visit
- SANDE symptoms score and change from baseline at each visit
- Symptoms score (5-point scale) and change from baseline at each visit, for each of the five symptoms assessed
- Occurrence and time to become markedly improved (defined as CFS score improvement of 2 or more on the modified Oxford scale at Month 12)
- TBUT and change from baseline at each visit
- Schirmer test and change from baseline at Month 12 visit
- Use of Artificial Tears over the last week and change from baseline at each visit

B) In Period 2:

- CFS score and change from Month 12 visit at each visit
- Conjunctival fluorescein staining score and change from Month 12 at each visit
- SANDE symptoms score and change from Month 12 visit at each visit
- Symptoms score (5-point scale) and change from Month 12 visit at each visit, for each of the five symptoms assessed
- TBUT and change from Month 12 visit at each visit
- Schirmer test and change from Month 12 visit at Month 24 and Month 36 visits
- Use of Artificial Tears (over the last week and change from Month 12 visit at each visit
- Occurrence and time to relapse (increase of CFS score of 2 or more on the modified Oxford scale)

C) In entire study:

- CFS score and change from baseline at each visit
- Conjunctival fluorescein staining score and change from baseline at each visit
- SANDE symptoms score and change from baseline at each visit
- Symptoms score (5-point scale) and change from baseline at each visit, for each of the five symptoms assessed
- TBUT and change from baseline at each visit
- Schirmer test and change from baseline at each visit

- Use of Artificial Tears over the last week and change from baseline at each visit

Quality of life:

In the randomised markedly improved population,

- Dry Eye related Quality of life Score (DEQS) overall score, and change from baseline at Month 6, Month 12, Month 18, Month 24, Month 30 and Month 36 Visits. Change from Month 12 will also be summarized for scores collected in Period 2.

Safety and Tolerability:

In the Safety population, safety and tolerability endpoints are:

- Intraocular pressure (IOP) and change from baseline at Month 12, Month 24 and Month 36 visits
- Best Corrected Distance Visual Acuity (BCDVA) and change from baseline at Month 6, Month 12, Month 24 and Month 36 visits visits.
- Incidence and severity of ocular and systemic adverse events (AEs) over the three-year study period.

Statistical methods:

Analysis Eye

All the efficacy analysis will be performed on the analysis eye only that fulfils all the criteria listed under the inclusion criteria #5. If both eyes are eligible, the eye with the highest baseline CFS score will be chosen. If not discriminant, the eye with the lowest Schirmer test value will be chosen. If not discriminant, the right eye will be chosen as the analysis eye.

Analysis Populations

Analysis populations are defined based on study period.

For Period 1:

- The **Full Analysis Set (FAS)** population consists of all enrolled subjects who received at least one dose of the study medication and had at least one post-baseline sign or symptom assessment of the study eye during Period 1. This will be the population used for efficacy analyses.
- The Per-Protocol Set (PPS) will be a subset of FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses.
- The **Safety population** consists of all patients enrolled in Period 1 who received at least one dose of the study medication and for whom any follow-up information is available. It will be the analysis population for safety analyses to be performed with subjects as treated.
- The following analysis subpopulation will be defined according to the treatment response to efficacy variables:

- **Markedly Improved Patients** are defined as FAS subjects who achieve CFS score improvement from baseline of 2 grades or more (unless if the patient had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more) at Month 12 visit.

For Period 2:

- The **FAS** population consists of all randomised patients who received at least one dose of the study medication and had at least one post-Month 12 sign or symptom assessment of the study eye during Period 2. This will be the population used for efficacy analyses.
- The Per-Protocol Set (PPS) will be a subset of FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses.
- The **Safety population** consists of all patients enrolled in Period 2 for whom any follow-up information is available. It will be the analysis population for safety analyses to be performed with subjects as treated.

For entire study:

- The **FAS** population consists of the Markedly Improved Patients who were randomised to IKERVIS in Period 2 and received at least one dose of IKERVIS in Period 2 and had at least one post-Month 12 sign or symptom assessment of the study eye during Period 2.
- The Per-Protocol Set (PPS) will be a subset of FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses.
- The **Safety population** consists of the Markedly Improved Patients who were randomised to IKERVIS in Period 2 and had at least one post-Month 12 sign or symptom assessment of the study eye during Period 2. It will be the analysis population for safety analyses to be performed with subjects as treated.

The Sjögren patients population will be specifically described separately for some analyses.

Analysis of Demographics and Baseline Characteristics

Descriptive summaries will be performed for demographic (including age, gender, race, ethnicity, female patients' menopausal status) and baseline characteristics variables (including Sjögren Disease status, time since diagnosis, past surgery or laser treatment in the analysis eye, and smoking status).

In addition, medical history (ocular and systemic) and prior and concomitant medication use will be summarised by treatment response status and for the overall population.

Analysis of Primary Efficacy and Safety Endpoints

Spearman correlation coefficient will be obtained between mean change from baseline in CFS score at visit X and SANDE symptoms score at each visit X+i for each FAS population in Period 1, Period 2, and entire study. For Period 1, visit X includes Day1, Month 3, Month 6, Month 9 and Month 12, and i is from 0 (Day 1) up to 4 (Month 12). For Period 2, X includes Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, and Month 36, and i is from 0 (Month 12) up to 8 (Month 36). Correlation coefficient will be analized by treatment group. For entire study, visit X includes all the scheduled visits from Day 1 to Month 36, and i is from 0 (Day1) up to 12 (Month 36). Missing data will not be imputed.

The incident rate of ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity, and ocular infection) will be estimated with its 95% CI for each safety population in Period 1, Period 2, and the entire study . The analysis for safety population in Period 2 will be conducted by treatment group.These rates will be compared to existing epidemiologic rates in a comparable population. Time to onset and time to resolution of the ocular complications will also be summarized.

Missing data will not be imputed.

Analysis of Secondary Efficacy Endpoints

For FAS population in Period 1, Period 2 and entire study, mean scores of CFS, conjunctival fluorescein staining, symptoms (SANDE and 5-point scale), TBUT, Schirmer test, artificial tear use and quality of life overall DEQS scores, and their change from baseline (Period 1 and Period 2) or from Month 12 (Period 2) will be summarized by analysis visit. The analysis for FAS population in Period 2 wil be performed by planned treatment groups.

Occurrence and time to relapse defined as an increase of CFS modified Oxford score of 2 or more will be summarized for FAS population in Period 2 by treatment group.

Survival analysis method will be employed to analyze the time to become Markedly Improved Patients for Period 1.

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

Missing data will not be imputed.

Analysis of Safety and Tolerability Endpoints

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

Adverse Events

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

AEs will be coded using the MedDRA dictionary. Frequencies and percentages will be given as follows: 1) Overall summary; 2) by system organ class and preferred term; 3) by system organ class, preferred term and maximal severity, 4) by system organ class, preferred term and relationship to study medication and study procedure, respectively, and 5) by system organ

class, preferred term, maximal severity, and relationship to study medication and study procedure, respectively.

Separate analyses will be performed AEs and serious adverse events (SAEs), and for ocular and systemic AEs and SAEs, respectively. Ocular AEs will be summarized for the analysis eye and the fellow eye separately.

Other Safety Assessments

Other parameters of safety assessments (e.g. slit lamp examination, BCDVA, and IOP) will be summarized at each time point of measurement. They will be summarized/ analysed for both the analysis eye and the fellow eye separately.

Interim Analysis

Once all patients will have performed their Month 12 visit or Early Termination visit, CFS, symptoms, quality of life and AEs will be analysed on clean data.

Mean and mean change from baseline (signs, symptoms and QOLs) will be provided. Correlation coefficient between mean change from baseline in CFS score at visit X and symptoms score at each visit X+i will be summarised.

Since the first 12 months of the study will be open-label study, no adjustment of alpha level and no Data Monitoring Committee will be needed for this study.

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	**Explanation**
AE	Adverse Event
AR	Adverse Reaction
AT	Artificial Tears
BCDVA	Best Corrected Distance Visual Acuity
CA	Competent Authority
CHMP	Committee for Medicinal Products for Human Use
CKC	Cetalkonium Chloride
CFS	Corneal Fluorescein Staining
CRO	Contract Research Organization
CsA	Ciclosporin
CSI	Case of Special Interest
DED	Dry Eye Disease
DEQS	Dry Eye-related Quality-of-Life Score
DEWS	Dry Eye Workshop
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoS	End of Study
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HLA-DR	Human Leucocyte Antigen-DR
ICH	International Conference on Harmonization

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MCT	Medium Chain Triglycerides
MGD	Meinbomian Gland Disease
OSDI	Ocular Surface Disease Index
PEO	Polyethylene Oxide
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PVU	Pharmacovigilance Unit
QD	Quaque Die
QOL	Quality of Life
RSI	Reference Safety Information
SAE	Serious adverse event
SANDE	Symptom Assessment iN Dry Eye
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SmPC	Summary of Product Characteristics
TBUT	Tear Breakup Time
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
VAS	Visual Analogue Scale

4. INTRODUCTION

Since the 2017 International Dry Eye Workshop (DEWS), the term dry eye disease (DED), also known as keratoconjunctivitis sicca, describes "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (DEWS 2017a)". The prevalence of DED ranges from 5% to 50% (DEWS 2017b).

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 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 possible vision loss (AAO 2013). Even though epidemiological data on DED long term evolution is rare, Petroutsos et al., 1992 showed, after a 6-year follow-up, a lower-bound of the estimate of the complication rate of 4% in severe patients (Petroutsos 1992).Thus for these severe diseases which need long-term treatment, clinical guidelines recommend using anti-inflammatory agents such as ciclosporin A (CsA) when lubricants are inadequate (DEWS 2017d).

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

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

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 with indication covers the need for a treatment of severe keratitis in dry eye patients.

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).

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. 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).

In the 12 month, double-masked, vehicle controlled, pivotal clinical trial (NVG10E117/SANSIKA study - Leonardi 2016), 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 randomised to one drop of IKERVIS® or vehicle daily at bedtime for 6 months. Patients randomised 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 (adjusted mean change from baseline was -1.764 with IKERVIS® vs. -1.418 with vehicle, p=0.037). The proportion of IKERVIS®-treated patients with at least a 3-grade improvement in CFS score at Month 6 (from 4 to 1, 0.5 or 0) was 35.6%, compared to 14.4% of vehicle-treated patients (p=0.001, post-hoc analysis). 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.

However tear film osmolarity was also analysed post hoc in a subgroup of patients with baseline levels >308 mOsms/L, a threshold known to be indicative of DED. A total of 55 patients met this criterion, 34 (22.1%) in IKERVIS® group and 21 (23.1%) in the vehicle group. IKERVIS® subgroup showed a significantly greater change from baseline at Month 6 than the vehicle subgroup (p=0.048), with the mean and median values of worst tear film osmolarity in IKERVIS® subgroup lower than 308 mOsms/L, whereas they remained slightly higher than this threshold in the vehicle subgroup

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

The most frequently reported treatment-related ocular adverse event was Instillation site pain, reported in a higher proportion of patients treated with IKERVIS® (29.2%) than with vehicle (8.9%) and was mostly mild (mild: 16.9%, moderate: 8.4%, and severe: 3.9% in the IKERVIS® group versus 4.4%, 2.2%, and 2.2%, respectively, in the vehicle group).

Upon completion of the SANSIKA study (Month 12 visit), patients were invited to enter a 24-month extension study (NVG12D122/Post-SANSIKA study), assessing the sustained efficacy of IKERVIS® after treatment discontinuation. Time to relapse (CFS score ≥4) was assessed following treatment discontinuation in patients from the SANSIKA study who had CFS improvement from grade 4 to ≤2 after 6 or 12 months of treatment with IKERVIS®. The Full Population included 66 patients. Of 62 patients who achieved a CFS ≤2 at the end of the SANSIKA study, 38 did not relapse and 24 (39%) relapsed during the 24-month period following IKERVIS® discontinuation; the latter (relapse) group comprised 35% of patients initially treated with IKERVIS® for 12 months in SANSIKA versus 47% of those treated for 6 months only. Patients spent the most time during the extension study at CFS scores of 1 or 2 (median duration 8.5 weeks and 14.7 weeks per year, respectively), indicating marked improvement, and less time at CFS scores of 3/4/5 (median time 2.03 weeks/0.0 weeks/0.0 weeks per year, respectively).

Of 23 patients eligible for safety analysis (patients who received the study treatment at least once), 5 ocular adverse events, reported in 5 patients (21.7%), were considered related to study treatment: 3 events of mild instillation site pain in 3 patients (13.0%) and eye discharge and foreign body sensation, each reported in 1 patient (4.3%).

In the 6 month, double-masked, vehicle controlled, supportive clinical trial (NVG06C103/SICCANOVE study - Baudouin 2017), 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 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).

The most common treatment-related adverse event was eye irritation, reported for 39 patients treated with IKERVIS® (16.1%) versus 6 patients (2.4%) with vehicle.

4.2. Rationale for the Proposed Study

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 following over 6 months and 12 months (SICCANOVE and SANSIKA, respectively) in adult patients with dry eye disease (keratoconjunctivitis sicca). However, these studies did not demonstrate a beneficial effect of IKERVIS® compared to Vehicle on symptoms. The CHMP acknowledged the difficulty to reach both endpoints (ie. significant effect on both signs and symptoms) as 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 DED patients with severe keratitis, a positive effect of a medication on symptoms may be impaired by the high degree of ocular surface damage which may reduce the corneal sensation. Additionally, there might be a delay in improvement of symptoms after improvement in signs are observed. Post-hoc analyses of SANSIKA support a lag time effect on symptoms: Spearman correlation coefficient between the change in CFS and OSDI overtime increased slightly from Month 1 to 6, even though it was not conclusive. Furthermore the pharmacologic and clinical profile of IKERVIS® suggests that it has the potential to provide consistent and efficacious anti-inflammatory effects, which may translate into a clinical benefit for the ocular surface.

In this context, the CHMP has recommended Santen to conduct a PAES (Post-Approval Efficacy Study) to further explore long term effects of IKERVIS® on signs, symptoms and ocular surface complications.

In order to establish IKERVIS® long-term efficacy and safety, the NVG14L127 trial proposes a 2-Period design: a one-year open label period (Period 1) to establish patient's response status according to the improvement on sign (ie. CFS); and Period 2 to assess, over 24 months, IKERVIS® long-term response in patients markedly improved after period 1, who will be randomised to receive either IKERVIS® or Vehicle, once daily.

4.3. Benefit Risk Assessment

The patients participating in the study will benefit from IKERVIS®, a product marketed in Europe and some Asian countries, 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 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 3 months) 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 profile is considered favourable.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objectives of the study are:

- To evaluate the long-term efficacy of a continuous treatment of IKERVIS® (1mg/mL ciclosporin) eye drops in adult dry eye disease (DED) patients with severe keratitis on corneal sign and DED symptoms, and to estimate the lag time (if any) to improvement in symptoms (if any) .
- To assess the ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity, and ocular infection) over the three-year study period.

5.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy parameters (signs and symptoms), the ocular surface complications, and the quality of life over treatment Periods 1 and 2.
- For 12-month markedly improved patients, to evaluate and compare signs and symptoms evolution in IKERVIS® group versus Vehicle group during the randomised period of the study (Period 2).
- To evaluate the safety and tolerability of IKERVIS® (1mg/mL ciclosporin) eye drops treatment over the three-year study period.

5.3. Endpoints

5.3.1. Primary Efficacy and Safety Endpoints

- The correlation between mean change from baseline in CFS score and SANDE symptoms score at each visit, and cross correlation of sign at visit X versus symptoms at visit X+i (i starting from 0), if any.
- Incident rate and time to onset of ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity and ocular infection)

5.3.2. Secondary Endpoints

5.3.2.1 Secondary Efficacy Endpoints

A) In Period 1:

- CFS score and change from baseline at each visit
- Conjunctival fluorescein staining score and change from baseline at each visit
- SANDE symptoms score and change from baseline at each visit

- Symptoms score (5-point scale) and change from baseline at each visit, for each of the five symptoms assessed
- Occurrence and time to become markedly improved (defined as CFS score improvement of 2 grades or more on the modified Oxford scale at Month 12)
- TBUT and change from baseline at each visit
- Schirmer test and change from baseline at Month 12 visit
- Use of Artificial Tears over the last week and change from baseline at each visit

B) In Period 2:

- CFS score and change from Month 12 visit at each visit
- Conjunctival fluorescein staining score and change from Month 12 at each visit
- SANDE symptoms score and change from Month 12 visit at each visit
- Symptoms score (5-point scale) and change from Month 12 visit at each visit, for each of the five symptoms assessed
- TBUT and change from Month 12 visit at each visit
- Schirmer test and change from Month 12 visit at Month 24 and Month 36 visits
- Use of Artificial Tears over the last week and change from Month 12 visit at each visit
- Occurrence and time to relapse (increase of CFS score of 2 or more on the modified Oxford scale)

C) In entire study:

- CFS score and change from baseline at each visit
- Conjunctival fluorescein staining score and change from baseline at each visit
- SANDE symptoms score and change from baseline at each visit
- Symptoms score (5-point scale) and change from baseline at each visit, for each of the five symptoms assessed
- TBUT and change from baseline at each visit
- Schirmer test and change from baseline at each visit
- Use of Artificial Tears over the last week and change from baseline at each visit

5.3.2.2 Quality of Life Endpoints

In the randomised markedly improved population, Quality of Life endpoints are:

- Dry Eye related Quality of life Score (DEQS) overall score, and change from baseline at Month 6, Month 12, Month 18, Month 24, Month 30 and Month 36 Visits. Change from Month 12 will also be summarized for scores collected in Period 2.

5.3.2.3 Safety and Tolerability Endpoints

In the Safety population, safety and tolerability endpoints are:

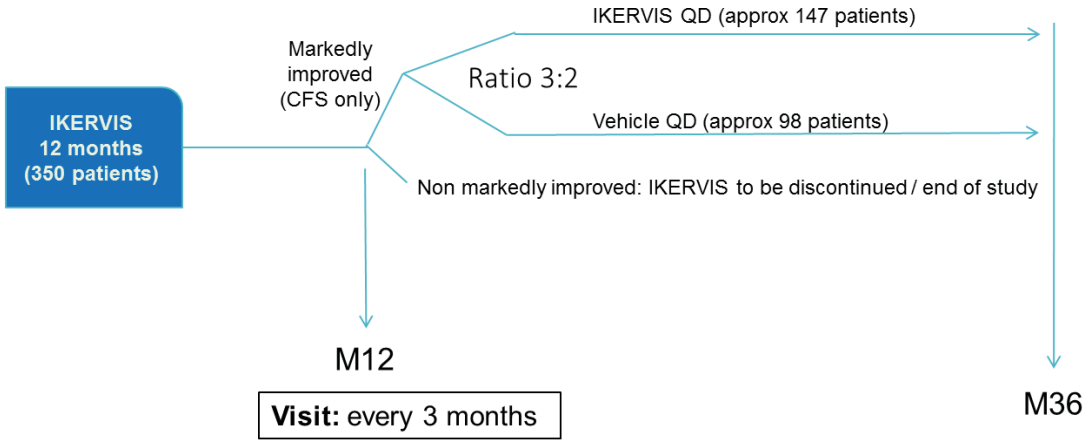
- Intraocular pressure (IOP) and change from baseline at Month 12, Month 24 and Month 36 visits
- Best Corrected Distance Visual Acuity (BCDVA) and change from baseline at Month 6, Month 12, Month 24 and Month 36 visits
- Incidence and severity of ocular and systemic adverse events (AEs) over the three-year study period.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

The proposed 36-month PAES is a prospective, interventional, multicentre study to explore the long-term evolution of signs and symptoms, and occurrence of complications in Dry Eye Disease (DED) patients with severe keratitis receiving IKERVIS® (1mg/mL ciclosporin) eye drops administered once daily (Table 3). In order to assess the response to IKERVIS® for DED patients with severe keratitis, after 12-month IKERVIS® (once daily) treatment, patients who have shown a marked improvement at Month 12 (as defined below) will be randomised to receive IKERVIS® or Vehicle (ration 3:2) in double-masked fashion (Figure 1):

Figure 1: Study Design and Schedule of Assessments



IKERVIS will be used with AT (same AT for all patients) up to 6 times per day

Marked improvement is defined as CFS score improvement from baseline of 2 grades or more on the modified Oxford scale [unless if the patient had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more] in the analysis eye.

Non markedly improved patients at Month 12 will be early terminated from the study.

6.2. Number of Subjects

A total of 350 patients are planned to be enrolled in approximately 52 trial sites.

It is expected that almost 70% of the included patients (approximately 245 patients) would enter the Period 2 (Double-masked randomised period) after Month 12.

6.3. Dose Adjustment Criteria

Not applicable.

6.3.1. Safety Criteria for Adjustment or Stopping Doses

Not applicable.

6.3.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

6.4. Criteria for Study Termination

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

- New information or other evaluation regarding the safety or efficacy of the study 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.

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

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

6.5. Demographic, Baseline Characteristics, and Medical History

Demographic information to be obtained will include baseline disease characteristics, date of birth or age, sex, alcohol and smoking status of the patient at Baseline.

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 ophthalmic medication within 1 year to signing of informed consent and any other medication stopped at or within 3 months prior to signing of informed consent.

Table 3: Study Design and Schedule of Assessments

	Baseline	**Period 1**		**Period 2**		**End of Study Visit**	
	Day 1	Month [a] 3 (D90), 6 (D180) and 9 (D270) (± 7 days)	Month [ah] 12 (D360) (± 7 days)	Month [a] 15 (D450), 21 (D630), 27 (810) and 33 (D990) (± 7 days)	Month [a] 18 (D540), 24 (D720) and 30 (D900) (± 7 days)	Month [a] 36 (D1080) (± 7 days)/ Early Termination	Unscheduled visit
Informed consent	X						
Demographic information	X						
Review of Inclusion/Exclusion Criteria	X						
Ocular and systemic medical history	X						
Previous and concomitant ocular and systemic medications	X	X	X	X	X	X	X
Artificial tears use [b]	X	X	X	X	X	X	X
Symptoms evaluation (SANDE) [c]	X	X	X	X	X	X	X
Symptoms evaluation (0-4 point scale) [c]	X	X	X	X	X	X	X
Quality of life questionnaire (DEQS)	X	X[d]	X		X	X	
Best corrected distance visual acuity (BCDVA)	X	X[d]	X		X	X	

	Baseline	**Period 1**		**Period 2**		**End of Study Visit**	
	Day 1	Month [a] 3 (D90), 6 (D180) and 9 (D270) (± 7 days)	Month [ah] 12 (D360) (± 7 days)	Month [a] 15 (D450), 21 (D630), 27 (810) and 33 (D990) (± 7 days)	Month [a] 18 (D540), 24 (D720) and 30 (D900) (± 7 days)	Month [a] 36 (D1080) (± 7 days)/ Early Termination	Unscheduled visit
Slit lamp examination	X	X[d]	X		X	X	
Tear break up time (TBUT)	X	X	X	X	X	X	X
Corneal and Conjunctival Fluorescein staining (Modified Oxford Scale)	X	X	X	X	X	X	X
Schirmer test (without anesthesia)	X		X		X[e]	X	
Intraocular Pressure (IOP)	X		X		X[e]	X	X
Urine pregnancy test (women of childbearing potential only)	X	X	X	X	X	X	
Adverse events (AEs)		X	X	X	X	X	X[f]
Registration of patients status in IWRS/IVRS (e.g. enrolment, randomisation, EoS/ET)	X		X			X	X
Compliance with study medication regimen		X	X	X	X	X	X

	Baseline	**Period 1**		**Period 2**		**End of Study Visit**	
	Day 1	Month [a] 3 (D90), 6 (D180) and 9 (D270) (± 7 days)	Month [ah] 12 (D360) (± 7 days)	Month [a] 15 (D450), 21 (D630), 27 (810) and 33 (D990) (± 7 days)	Month [a] 18 (D540), 24 (D720) and 30 (D900) (± 7 days)	Month [a] 36 (D1080) (± 7 days)/ Early Termination	Unscheduled visit
Dispensation of unpreserved artificial tears	X	X	X	X	X		X [g]
Dispensation of **open-label study medication**	X	X					X [g]
Dispensation of **masked study medication**			X[hi]	X[i]	X[i]		X [g]
Collection of used study medication	X	X	X	X	X	X	X

[a] *Months of 30 days.*
[b] *Artificial tears (AT) use assessed by questioning the patient at each study visit.*
[c] *Symptom of dry eye will be evaluated at each study visit by completing SANDE questionnaire and 5 symptoms using a 0-4 point scale..*
[d] *QoL and BCDVA will NOT be assessed and slit lamp examination will not be performed at Month 3 and 9.TBUT and corneal and conjunctival fluorescein staining which will be performed at each visit.*
[e] *Schirmer test and IOP will NOT be performed at Month 18 and 30 visits.*
[f] *Record AEs if the unscheduled visit is after the first study drug administration.*
[g] *Dispensation of study medication and/or unpreserved artificial tears if necessary.*
[h] *Randomisation of markedly improved patients at Month 12 visit.*
[i] *Dispensation of masked study medication (IKERVIS® or Vehicle).*

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject 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 has signed and dated 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. At least 4 weeks of use of tear substitutes prior to the Baseline Visit
5. DED patients with severe keratitis defined as the following:
    - CFS score of 3, 4 or 5 on the modified Oxford scale in at least one eye at Baseline Visits,

    AND

    - Schirmer test without anaesthesia scored <10 mm/5min in the same eye at Baseline Visit,

    AND

    - At least two moderate to very severe symptoms of dry eye disease with a score ≥2 (severity graded on a 0 to 4 grade scale), among the following symptoms: burning/stinging, foreign body sensation, eye dryness, eye pain and blurred/poor vision at Baseline Visit.
6. Patient must be willing and able to undergo and return for scheduled study-related examinations.

7.2. Subject Exclusion Criteria

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

1. Active herpes keratitis or history of ocular herpes.
2. History of ocular trauma or ocular infection (viral, bacterial, fungal, protozoal) within 90 days before the Baseline Visit.
3. Any ocular diseases other than DED requiring topical ocular treatment during the course of the study. Patients taking preservative-free IOP lowering medications are eligible for study enrolment.
4. Concurrent ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye.

5. Anticipated use of temporary punctal plugs during the study. Patients with punctal plugs placed prior to the Baseline Visit are eligible for enrolment; however, punctal plugs must remain in place during the study.
6. Best corrected distance visual acuity (BCDVA) score $\leq$ 20/200 Snellen in each eye.
7. 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 or judged by the investigator to be incompatible with the study (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections, ocular infection…).
8. Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein, etc.).
9. History of ophthalmic malignancy
10. History of malignancy (other than ophthalmic) in the last 5 years.
11. 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.
12. Use of topical ciclosporin in the past 3 months prior to Baseline visit.
13. Any change in systemic immunosuppressant drugs within 30 days before the Baseline Visit or anticipated change during the course of the study.
14. Pregnancy or lactation at the Baseline Visit.
15. Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomised partner) from the Baseline Visit throughout the conduct of the study treatment periods and up to 2 weeks after the study end. Post-menopausal women (two years without menstruation) do not need to use any method of birth control.
16. Participation in a clinical trial with an investigational substance within the past 30 days prior to Baseline Visit.
17. Participation in another clinical study at the same time as the present study.

7.3. Screen Failure

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

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

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

7.4. Subject Discontinuation or Withdrawal Criteria

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

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. Patients discontinued for drug–related AE(s) will be followed-up after patient's discontinuation until the event is resolved, stabilized or a final assessment can otherwise be done by the investigator.
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. In case of a patient lost-to-follow-up, the investigator must do his/her best to contact the patient initially by phone, then by letter, and finally by certified mail. If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or his/her general physician. These attempts must be documented and associated documentation filed in the patient medical chart.
4. Voluntary withdrawal. The patient (or patient's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The Sponsor, 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 12.2.1.5.
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 is chosen (e.g. moving…) and specific primary reason should be recorded in the "specify" field of the eCRF.

7.5. Procedures for Discontinuation or Withdrawal of a Patient

The investigator may terminate a patient's study participation at any time during the study when the patient meets the study withdrawal criteria described in Section 7.4. Efforts should be made to perform all procedures scheduled for the End of Study Visit (Month 36/Early Termination). Discontinued patients will not be replaced.

7.6. Completed Enrollment

The study enrolment will be considered as completed when the desired number of at least 350 included patients is reached.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug and Vehicle

IKERVIS® is a sterile, ophthalmic cationic oil-in-water emulsion containing 1 mg/ml CsA. Vehicle is a sterile, ophthalmic cationic oil-in-water emulsion containing no active substance CsA.

IKERVIS® and vehicle 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 stabilised 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 for injections: as diluents and the main emulsion component.

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

The manufacturer will be Excelvision located in Annonay, France.

8.2. Concomitant Medications/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 other than those provided by the Sponsor.
- Use of any topical ocular treatments other than the study medication and preservative-free IOP lowering agents.
- Insertion of temporary punctal plugs during the study.

- Initiation or change in the dose of any of the following 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 deviation.

8.3. Treatment Compliance

Patient compliance will be assessed at each visit by investigator by questioning the patient and comparison to drug accountablity. All reported incidents of the lack of compliance will be recorded on the eCRF with the reasons. If a patient is persistently noncompliant with the study medication, the patient should 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.

8.4. Randomisation and Masking

Period 1 of the study is open-label, single arm treatment with IKERVIS®. No randomization is needed in Period 1 (from Baseline for the first 12 months of treatment).

At the beginning of Period 2, (ie. the Month 12 visit), subjects who achieve a marked improvement (ie. CFS score improvement from baseline of 2 grades or more [unless if the patient had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more]) will be randomly assigned (by the IWRS/IVRS) in a 3:2 ratio to receive either IKERVIS® or Vehicle for two years in a double-masked fashion. The randomization will be stratified by pooled country or region (Europe vs. non-Europe) pending the distribution of eligible subjects for Period 2, and the permuted block randomization will be used within each strata.

The randomization schedule will be generated and implemented using central randomization via Interactive Response Technology (Rave RTSM). Each randomized subject will receive numbered study medication kits as assigned by Rave RTSM.

Treatment assignments during the Double-Masked Treatment Period will be masked to Santen employees (except Drug Supply personnel), study subjects, and Investigators. The investigator should try to avoid breaking the masking codes. However**, IN CASE OF EMERGENCY ONLY, (i.e. SERIOUS ADVERSE EVENT (SAE) AND ONLY WHEN THIS INFORMATION INFLUENCES THE PATIENT'S MANAGEMENT),** the investigator is entitled to unmask the patient by using IWRS, in order to obtain the study medication information (i.e. IKERVIS® or vehicle) to immediately start the appropriate treatment [to be recorded in the source data and eCRF (electronic Case Report Form)]. A record will be made of the date, time and reason for breaking the code. The investigator should inform the sponsor immediately after unsmasking. The details of this unmasking procedure will be described in a separate document. Patients unmasked for the management of a SAE will be discontinued from the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Refer to section 8.1.

9.2. Study Drug Packaging and Labeling

Open-label study treatment of Period 1

For all the patients during the first 12-month period, IKERVIS® will be provided at each quarterly visit.

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

- 22 aluminum pouches (i.e. 110 single-dose containers) of IKERVIS® will be placed together in a sealed cardboard box.

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

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

Double-masked study treatment sequence of Period 2

For the markedly improved patients at Month 12 visit, after randomisation, the investigational medical products (IKERVIS® or its Vehicle) will be supplied in double masked polyethylene single-dose containers presented in sealed laminate aluminum pouch package (1 pouch contains 5 single-dose containers).

- 22 aluminum pouches (i.e. 110 single-dose containers) of IKERVIS® or its Vehicle will be placed together in a sealed cardboard box. One identical box will be dispensed at each quarterly visit.

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

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

9.3. Study Drug 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**.

Any temperature excursion of study drug should be notified to the sponsor and the supplies placed in quarantine before further instruction is received from the sponsor. 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 below 30°C and it must not be freezed. 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.

9.4. Study Drug Preparation

Not applicable.

9.5. Administration

The investigational product will be instilled once daily into the affected eye(s), at bedtime.

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

Under no circumstances will the investigator allow the study products to be used other than directed by the protocol. All dispensations and returns of study medication have to be documented in the investigator's file provided by the Sponsor.

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

9.6. Study Drug Accountability and Destruction

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

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

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.

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

10. SCHEDULE OF OBSERVATIONS AND PROCEDURES

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

The study period will include the initial Baseline Visit (Day 1), the 12-month open-label study treatment phase, and then the two-arm randomised double-blind design up to Month 36 (D1080) study visit.

10.1. Treatment Phase

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

10.1.1. Baseline: Day 1

- Informed consent
- Inclusion/exclusion criteria review
- Demographics
- Ocular and systemic medical history
- Previous and concomitant ocular and systemic medications [including artificial tears (AT) usage]
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- Quality of life questionnaires (DEQS)
- BCDVA
- Slit lamp examination
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- Schirmer test (without anaesthesia)
- IOP
- Urine pregnancy test (women of childbearing potential only)
- Record adverse events (AEs)
- Verify inclusion and exclusion criteria based on evaluations just performed:
    - Patients **fulfilling** the inclusion / exclusion criteria will discontinue all previous treatments related to dry eye including artificial tears and any prohibited ocular treatments and receive the study treatment for the next 3 months. The enrolment will be registered in IWRS/IVRS Rave RTSM.
    - Patients **not fulfilling** the inclusion / exclusion criteria will become screen failure

- Dispensation of study medication and unpreserved artificial tears for a 3-month period
- Patients will be scheduled to return to the clinic in 3 months (90 days ± 7 days) for the next study visit

10.1.2. Month 3 (D90) (±7 days), Month 6 (D180) (±7 days), and Month 9 (D270) (±7 days)

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Urine pregnancy test (women of childbearing potential only)
- Record adverse events (AEs)
- Assessment of Artificial tears use by questioning the patient
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- Quality of life questionnaires (DEQS) ONLY at Month 6 (D180)
- BCDVA ONLY at Month 6 (D180)
- Slit lamp examination ONLY at Month 6 (D180)
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Assessment of compliance to study medication
- Dispensation of study medication and unpreserved artificial tears for a 3-month period
- Patients will be scheduled to return to the clinic in 3 months (90 days ± 7 days) for the next study visit

10.1.3. Month 12 (D360) (±7 days)

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Urine pregnancy test (women of childbearing potential only)
- Record adverse events (AEs)
- Assessment of Artificial tears use by questioning the patient
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- Quality of life questionnaires (DEQS)
- BCDVA

- Slit lamp examination
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- Schirmer test (without anaesthesia)
- IOP
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Assessment of compliance to study medication
- Assessment of patient's improvement status. Access to IWRS/IVRS system- Rave RTSM-
  - To either randomise the markedly improved patient to receive IKERVIS® or vehicle in a double-masked fashion.
  - Or to report a withdrawal of not markedly improved patient.
- Dispensation of study medication and unpreserved artificial tears for a 3-month period
- Patients will be scheduled to return to the clinic in 3 months (90 days $\pm$ 7 days) for the next study visit

10.1.4. Month 15 (D450) (±7 days), Month 21 (D630) (±7days), Month 27 (D810) (±7 days), and Month 33 (D990) (±7 days)

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Urine pregnancy test (women of childbearing potential only)
- Record adverse events (AEs)
- Assessment of Artificial tears use by questioning the patient
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Assessment of compliance to study medication
- Dispensation of study medication and unpreserved artificial tears for a 3-month period
- Patients will be scheduled to return to the clinic in 3 months (90 days $\pm$ 7 days) for the next study visit

10.1.5. Month 18 (D540) (±7 days), Month 24 (D720) (±7 days), and Month 30 (D900) (±7 days)

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Urine pregnancy test (women of childbearing potential only)
- Record adverse events (AEs)
- Assessment of Artificial tears use by questioning the patient
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- Quality of life questionnaires (DEQS)
- BCDVA
- Slit lamp examination
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- Schirmer test (without anaesthesia) ONLY at Month 24 (D720)
- IOP ONLY at Month 24 (D720)
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Assessment of compliance to study medication
- Dispensation of study medication and unpreserved artificial tears for a 3-month period
- Patients will be scheduled to return to the clinic in 3 months (90 days $\pm$ 7 days) for the next study visit

10.1.6. Month 36 (D1080) (±7 days)/End of Study/Early Termination

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Urine pregnancy test (women of childbearing potential only)
- Record adverse events (AEs)
- Assessment of Artificial tears use by questioning the patient
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- Quality of life questionnaires (DEQS)
- BCDVA

- Slit lamp examination
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- Schirmer test (without anaesthesia)
- IOP
- Collection of used/not used study medication containers and unpreserved artificial tear bottles
- Assessment of compliance to study medication
- Registration of End of Study or Early Termination in IWRS/IVRS Rave RTSM

10.1.7. Unscheduled Visit

An Unscheduled visit will be performed if required between two scheduled visits (e.g: patient's request, check of medical event needed, but not for routine care that is not related to the protocol) and the reason for such a visit will be recorded in the CRF. In this case, the investigator will be asked to perform all the following procedures and examinations at his discretion (which must be performed in the chronological order defined below):

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage]
- Record adverse events (AEs)
- Assessment of Artificial tears use by questioning the patient
- Symptoms evaluation by completing SANDE questionnaire
- Symptoms evaluation by completing the 0-4 point scale
- TBUT
- Corneal and conjunctival fluorescein staining (modified Oxford scale)
- IOP
- Collection of used/not used study medication containers and unpreserved artificial tear bottles, if any, or ask for patient's compliance with study medication regimen
- If needed, dispensation of study medication and unpreserved artificial tears for a 3-month period
- Patients will will be scheduled to return to the clinic at next planned scheduled visit

If necessary (e.g. to follow up an AE) the investigator may schedule further visits at his discretion.

In case of patient's premature study discontinuation:

- the investigator will be asked to perform all the examinations and assessments scheduled for the End of Study Visit (Month 36/Early Termination)

- the investigator will ensure that used and unused study medication for the study period has been collected from the patient by the appointed person at the study site

11. ASSESSMENT OF EFFICACY

11.1. Corneal and Conjunctival Fluorescein Staining

Corneal and conjunctival fluorescein staining will be assessed immediately following the TBUT. Reading will be performed between 1 and 4 minutes after fluorescein instillation for the TBUT, to ensure that the dye does not diffuse into stroma blurring the discrete margin of any staining defects. 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 (provided by the Sponsor) will be graded using the modified Oxford scale (7-point ordinal scale, score 0, 0.5, and 1 to 5 per area [cornea + nasal and temporal conjunctiva]) for cornea and conjunctiva separately, see Appendix A-IV. On this modified scale, the score 0 corresponds to no staining dots and the score 0.5 corresponds to one staining dot per area.

A CFS grade of 0 represents complete corneal clearing.

A negative change score from baseline (Period 1) or from Month 12 (Period 2) will indicate improvement.

11.2. Tear Break-Up Time

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

The TBUT value will be the average of the 2 or 3 measurements.

A positive change from baseline (Period 1) or from Month 12 (Period 2) will indicate improvement.

11.3. 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 will be removed and the length of the tear absorption on the strip will be measured.

A positive change from baseline (Period 1) or from Month 12 (Period 2) will indicate improvement.

11.4. 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-III.

11.5. 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 over the last week, 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 Baseline Visit patients will be allowed to instill 1 unpreserved artificial tear drop, up to six 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.

11.6. Symptoms Evaluation (SANDE)

The self-administered Symptom Assessment iN Dry Eye (SANDE) questionnaire must be completed by the patient him/herself.

SANDE questionnaire will be used to score both severity and frequency of dry eye symptoms (see Appendix A-I). This 2-item frequency- and severity-based visual analogue scales (0-100mm VAS ranging respectively from" rarely" to "all the time", and from "very mild" to "very severe") is short and quick, and provides reliable measure for DED symptoms assessment. Symptoms will be evaluated for both eyes together.

A negative change from baseline (Period 1) or from Month 12 (Period 2) will indicate an improvement in dry eye disease symptoms.

11.7. Symptoms Evaluation Using 0-4 Point Scale

The 5-point Likert scales are a self-administered questionnaire and must be completed by the patient him/herself.

Burning/stinging, foreign body sensation, eye dryness, photophobia, pain and blurred/poor vision, will be assessed by the study patients using a 5-point Likert scale from none to very severe (0 to 4). Symptoms will be evaluated for both eyes together. (see Appendix A-II).

A decrease in symptom score from baseline (Period 1) or from Month 12 (Period 2) will indicate improvement of the symptom.

11.8. Quality of Life Questionnaires

11.8.1. Dry Eye symptoms-related Quality of Life Score (DEQS)

The DEQS consists of 15 items related to dry eye symptoms and influence on daily life, and the overall degree of Quality of Life impairment is calculated as a summary score (0 to 100).

The responses to DEQS are to be obtained from the patient through a self-administered format (completed by the patient him/herself). (see Appendix A-V).

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Best Corrected Distance Visual Acuity (BCDVA)

Best corrected distance VA will be measured with the patient's best correction and recorded using a Snellen chart.

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

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

All tonometers must be calibrated according to manufacturer's instructions .

12.1.3. Adverse Events (AEs)

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

12.1.4. Pregnancy Screen

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

Patients must have a negative urine pregnancy test at Baseline and throughout the study.

12.2. Adverse Events and Other Safety Information

12.2.1. Definitions

12.2.1.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a study drug. An AE does not necessarily have a causal relationship with the study drug. For this study, the study drugs are IKERVIS® and vehicle. Regardless of causality to the

study treatment, an AE can be an unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment.

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

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

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

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

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

12.2.1.2. Serious Adverse Event (SAE)

A serious AE (SAE) may occur during any study phase (ie, baseline, treatment, or follow-up). SAE must fulfil one or more of the following criteria:

- Results in death
- It is immediately life-threatening*
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above (including sight-threatening** events and cancer or neoplasm of any type).

*Herein 'Life-threatening' refers to an event in which the patient was at immediate risk of death at the time of event; it does not refer to an event which hypothetically might have caused death.

**Similarly 'Sight-threatening' refers to an event in which the patient was at immediate risk of losing sight; it does not refer to an event which hypothetically might have caused losing of sight.

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

- Adverse Events that caused a decrease in visual acuity > 6 lines (compared with the last assessment of visual acuity at the last visit)

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

12.2.1.3. Case of Special Interest (CSI)

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

- Non-serious AEs requiring (24 h) reporting to the sponsor:
  - Corneal ulceration
  - Decrease in visual acuity of 3 to 6 lines (compared with the last assessment of visual acuity at the last visit)
- Overdose of study drug
  - Administration of a quantity of a medicinal product exceeding the dose defined in the study protocol.
- Misuse of study drug
  - 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 or patient.
- Abuse of study drug
  - Persistent or sporadic, intentional excessive use of medicinal product which is accompanied by harmful physical or psychological effects.

12.2.1.4. Pregnancy Reports

It is required that women of childbearing potential are using a medically acceptable, highly effective method of birth control during the study and up to 2 weeks after the study end. Any pregnancy occurring during the study or within 14 days of completing the study should be reported to Santen EMEA Pharmacovigilance Unit (PVU) and the subject will be removed from the study.

Pregnancies of partners to study subjects with paternal drug exposure must also be reported to Santen EMEA PVU.

12.2.2. Assessment of Adverse Events

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

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

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

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

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

12.2.2.1. Seriousness

The seriousness of each AE must be assessed by the investigator according to the criteria set for SAEs in section 12.2.1.2. If the event does not meet the criteria of a SAE, it is assessed as non-serious.

12.2.2.2. Causality to Study Drug or Artificial Tears

An investigator who is qualified in medicine must make the determination of causality to the study drug and artificial tears provided by the Sponsor for each AE occurred during the study as defined in section 12.2.2. The following categories shall be used:

Related: There is a reasonable possibility that the AE may have been caused by the study drug or artificial tears.

Not related: There is no reasonable possibility that the AE may have been caused by the study drug or artificial tears.

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug or artificial tears. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated”. If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study drug (or artificial tears) and the occurrence of the AE, then the AE should be considered “related”.

12.2.3. Relationship to Study Procedures

The relationship to study procedures (e.g., Schirmer test) should be determined for AE using the following categories:

Related: There is a reasonable possibility that an event may have been caused by a study procedure.

Not Related: There is no reasonable possibility that an event may have been caused by a study procedure.

12.2.3.1. Severity of the Adverse Event

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may not be considered serious.

12.2.3.2. Expectedness

AEs will be evaluated as to whether they are expected or unexpected. The assessment is performed by the sponsor and in this study it is based on the list of adverse reactions in the section 4.8 ‘Undesirable Effects’ in the approved IKERVIS® EU Summary of Product Characteristics (SmPC) which acts as a Reference Safety Information (RSI).

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

12.2.4. Reporting of Safety Information

12.2.4.1. Reporting of Adverse Events

All serious and non-serious AEs including non-serious AEs considered to be of special interest (CSI) by sponsor (in Section 12.2.1.3), must be reported on the adverse event electronic case report form (AE e-CRF). In addition, SAEs and non-serious AEs, which have been considered to be CSI, must be reported expeditedly to the sponsor (Section 12.2.4.3).

For each AE, the investigator will evaluate and report

- The date site became aware of the event
- The AE/safety information term (verbatim)
- the onset date

- outcome of event
- The end date, if applicable
- severity
- location (e.g. right/left eye, both eyes, or not applicable if non ocular event)
- causality to study drug (Related / Not related)
- causality to artificial tears
- relationship to study procedures
- action taken with the study drug (for AEs only)
- seriousness
- Treatment medications, if applicable
- Historical/concurrent medical conditions relevant for the AE
- whether or not AE caused the patient to discontinue the study.

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

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

12.2.4.2. Reporting of Case of Special Interest and Pregnancy

Other CSIs (non-serious AEs covered in the Section 12.2.1.3) or spontaneously reported pregnancy in a patient or in a partner to the patient must be recorded in the source documents at the investigation site and reported expeditedly to Santen EMEA PVU (Section 12.2.4.3).

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

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

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

12.2.4.3. Expedited reporting

All SAE, CSI and Pregnancy reports must be reported to Santen EMEA PVU immediatey but no later than within 24 hours of the first awareness of the event. The investigator must complete, sign and date the SAE (or CSI/Pregnancy) pages, verify the accuracy of the information recorded on the SAE (or CSI/Pregnancy) pages, and send a copy by e-mail or fax to Santen EMEA PVU:

Santen EMEA, Pharmacovigilance Unit (PVU)

Email to safetyEU@santen.com **or**

Fax to +358 3 318 1060

(Phone +358 3 284 8625)

The sponsor records all SAE, CSI and Pregnancy reports in the safety database of Santen.

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

The sponsor is responsible for ongoing safety evaluation of the study drug. If there is at least a reasonable possibility that the event is related to the study drug and it is both serious and unexpected (SUSAR), the sponsor shall initiate expedited reporting according to applicable reporting requirements to all relevant parties, including regulatory authorities and ethics committees. Reporting responsibilities are described in the study specific safety management plan.

Investigators will also be notified of all suspected, unexpected serious study drug –related adverse reactions (SUSARs) that occur during the clinical trial.

12.2.5. Documentation of Safety Information

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

13. STATISTICS

13.1. General Considerations

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

All data manipulations and descriptive summaries will be performed using SAS Version 9.4 or later. The FDA guidance on case report tabulations (annotated eCRFs, SAS datasets, metadata, and SAS programs) in electronic submission will be followed. Data definition tables will be created for SDTM and ADaM datasets, separately.

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

13.1.1. Sample Size

This sample size of this study is not planned from a formal sample size calculation since formal statistical hypothesis testing will not be performed for the primary endpoints.In this study, we plan to enroll 350 subjects. Of the 350 subjects, it is estimated that approximately 70% (245 subjects) would become markedly improved in CFS after Month 12 and enter the Period 2 (Double-masked randomised period), based on Santen previous IKERVIS studies. With a 3:2 randomization allocation ratio, a sample size of 147 for IKERVIS® and 98 for Vehicle will allow to detect a difference of 0.4 or more in CFS score with 80% power assuming the standard deviation of the difference is 1.10.

Petroutsos *et al*. (1992) showed that after 6 years of follow-up on DED patients, a lower-bound of the estimated complication rate was 4% in severe DED patients. In the current study, 350 subjects treated with IKERVIS® for at least one year would have 95% power to detect at least one ocular complication that occurs at 1% rate with type I error rate of 0.05.

13.1.2. Statistical Hypotheses and Level of Significance

There will be no statistical hypotheses for the primary and secondary endpoints.

13.1.3. Analysis Eye

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

All the efficacy analysis will be performed on the analysis eye only.

13.2. Analysis Populations

Analysis populations are defined based on study period.

For Period 1:

- The **Full Analysis Set (FAS)** population consists of all enrolled subjects who received at least one dose of the study medication and had at least one post-baseline sign or symptom assessment of the study eye during Period 1. This will be the population used for efficacy analyses.
- The **Per-Protocol Set (PPS)** will be a subset of FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses.
- The **Safety population** consists of all patients enrolled in Period 1 who received at least one dose of the study medication and for whom any follow-up information is available. It will be the analysis population for safety analyses to be performed with subjects as treated.
- The following analysis subpopulation will be defined according to the treatment response to efficacy variables:
    - **Markedly Improved Patients** are defined as FAS subjects who achieve CFS score improvement from baseline of 2 grades or more (unless if the patient had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more) at Month 12 visit.

For Period 2:

- The **FAS** population consists of all randomised patients who received at least one dose of the study medication and had at least one post-Month 12 sign or symptom assessment of the study eye during Period 2. This will be the population used for efficacy analyses.
- The **PPS** will be a subset of FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses.The **Safety population** consists of all patients enrolled in Period 2 for whom any follow-up information is available. It will be the analysis population for safety analyses to be performed with subjects as treated.

For entire study:

- The **FAS** population consists of the Markedly Improved Patients who were randomised to IKERVIS in Period 2 and received at least one dose of IKERVIS in Period 2 and had at least one post-Month 12 sign or symptom assessment of the study eye during Period 2. This will be the population used for efficacy analyses.
- The **PPS** will be a subset of FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses.
- The **Safety population** consists of the Markedly Improved Patients who were randomised to IKERVIS in Period 2 and had at least one post-Month 12 sign or symptom

assessment of the study eye during Period 2. It will be the analysis population for safety analyses to be performed with subjects as treated.

13.3. The Sjögren patients population will be specifically described separately for some analyses. Analysis of Demographics and Baseline Characteristics

Descriptive summaries will be performed for demographic (including age, gender, race, ethnicity, female patients' menopausal status) and baseline characteristics variables (including Sjögren Disease status, time since diagnosis, past surgery or laser treatment in the analysis eye, and smoking status) by each FAS and safety population in Period 1, Period 2 and entire study.

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

13.4. Analysis of Primary Endpoints

Spearman correlation coefficient and p-values will be obtatined for the correlation analysis between mean change from baseline in CFS score at visit X and symptoms score at each visit X+i for each FAS population in Period 1, Period 2 and entire study. For Period 1, visit X includes Day1, Month 3, Month 6, Month 9 and Month 12, and i is from 0 (Day 1) up to 4 (Month 12). For Period 2, X includes Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, and Month 36, and i is from 0 (Month 12) up to 8 (Month 36). Correlation coefficient will be analized by treatment group. For entire study, visit X includes all the scheduled visits from Day 1 to Month 36, and i is from 0 (Day1) up to 12 (Month 36). Missing data will not be imputed.

The incident rate of ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity, and ocular infection) will be estimated with its 95% CI for each safety population in Period 1, Period 2, and the entire study. The analysis for safety population in Period 2 will be conducted by treatment group. The incident rates will be compared to existing epidemiologic rates in a comparable population. Time to onset and time to resolution of the ocular complications will also be summarized. Missing data will not be imputed.

Subgroup analysis by randomization stratification factor will be conducted to test the homogeneity of treatment effects in Period 2.

13.5. Analysis of Secondary Endpoints

For FAS population in Period 1, Period 2 and entire study, mean scores of CFS, conjunctival fluorescein staining, symptoms (SANDE and 5-point scale), TBUT, Schirmer test, artificial tear use and quality of life (DEQS) score, and their change from baseline (Period 1 and Period 2) and change from Month 12 (Period 2) will be summarized by analysis visit. The analysis for FAS population in Period 2 will be conducted by treatment groups.

Occurrence and time to relapse defined as an increase of CFS modified Oxford score of 2 or more will be summarized for FAS population in Period 2 by treatment group.

Survival analysis method will be employed to analyze the time to become Markedly Improved Patients in Period 1.

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

Missing data will not be imputed.

13.6. Analysis of Safety and Tolerability Endpoints

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

13.6.1. Adverse Events

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

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

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

13.6.2. Ocular Surface Complications

Ocular surface complications will be analised as one of the primary endpoints. See details in section 13.4.

13.6.3. Other Safety Assessments

Other parameters of safety assessments (e.g. slit lamp examination, BCDVA, and IOP) will be summarised at each time point of measurement for each safety population in Peirod 1, Period 2 and entire study. They will be summarised/ analysed for the analysis eye and the fellow eye separately. The analysis for safety population in Period 2 will be conducted by treatment group.

13.7. Interim Analysis

Interim analysis will be conducted once all patients will have performed their Month 12 visit or withdrawal visit, CFS, symptoms (SANDE and 5-point scale), quality of life and AEs will be analyzed on clean data. The purpose of the interim analysis is to present signs, symptoms and QoL data as well as calculation of correlation and lag time in FAS population in Period 1 and in patients with a Sjögren disease.

Mean and mean change from baseline (signs, symptoms and QOLs) will be provided. Correlation coefficient between mean change from baseline in CFS score at visit X and symptom score at each visit X+i will be analized, where X includes scheduled visits from Day 1 to Month 12, and i is from 0 up to 4.

Since the first 12 months of the study will be open-label study, no adjustment of alpha level and no Data Monitoring Committee will be needed for this study.

13.8. Handling of Missing Values

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

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

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of theSponsor will visit the investigational study site to:

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

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

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

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

14.2. Audits and Inspections

Authorised representatives of Santen, a regulatory authority (national or foreign), an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Santen immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

A written favourable opinion of IRB or IEC (as appropriate) must be obtain prior starting the study. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Santen may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

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

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

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Please see Appendix B- "Responsibilities of the Investigator" and Appendix E- Declaration of Helsinki.

16.3. Written Informed Consent

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

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

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

17. DATA HANDLING AND RECORD KEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

17.3. Source Documents

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

- Mention of patient's participation in the study, patient code and treatment number, date and process of signature of informed consent form
- Demographic data (date of birth, sex, name)
- Past medical and surgery history
- Past and recent treatments
- Concomitant treatments at inclusion
- Change in concomitant treatments throughout the study
- Date of each study visit
- Date of the final visit
- Date and reason of premature withdrawal
- All data related to study procedures
- Any non-serious AEs, SAEs and CSIs occurred during the time course of the study and study drug-related SAEs which occurred after the completion of the study
- Any pregnancy occurring during the study or within 14 days of completing the study

- Any data that could be judged by the Investigator as relevant

This list is not exhaustive.

17.4. Data Collection

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

18. PUBLICATION POLICY

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. 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.

19. LIST OF REFERENCES

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20. APPENDICES

Appendix A-I Symptom Assessment iN Dry Eye (SANDE) questionnaire

Symptom Assessment iN Dry Eye (SANDE) questionnaire is based on visual analog scales (VAS) to quantify both severity and frequency of dry eye symptoms[1,2].

The patient will thus be asked to rate severity and frequency of dry eye symptoms by placing a vertical mark on the horizontal line to indicate each level on the 100 mm line. The measurement of symptom frequency ranges from "rarely" to "all of the time", and the symptom severity ranges from "very mild" to "very severe". Symptoms will be evaluated for both eyes together.

Please complete the following questions regarding the frequency and severity of your dry eye symptoms

1. Frequency of symptoms

Please place a vertical mark over the line to indicate how often, on average, your eyes feel dry and/or irritated:

Rarely ——————————————— All the time

2. Severity of symptoms

Please place a vertical mark over the line to indicate how severe, on average, you feel your symptoms of dryness and/or irritation:

Very mild ——————————————— Very severe

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

[1] Gulati A, Sullivan R, Buring JE, et al. Validation and repeatability of a short questionnaire for dry eye syndrome. Am J Ophthalmol 2006; 142:125 31

[2] Schaumberg DA, Gulati A, Mathers WD, et al. Development and validation of a short global dry eye symptom index. Ocul Surf 2007; 5:50 7

Appendix A-II Evaluation of 5 symptoms of DED using the 5-point Likert scale

The 5-point Likert scales are a self-administered questionnaire and should be completed by the patient. The patient will be asked to rate the severity of the 5 symptoms by ticking the box for each symptom that best represents his/her answer. Symptoms will be evaluated for both eyes together.

SYMPTOMS	None	Mild	Moderate	Severe	Very severe
Burning/stinging	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4
Foreign body sensation	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4
Eye dryness	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4
Eye pain	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4
Blurred/poor vision	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4

Appendix A-III 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 localised to a small region of the lid(s) margin OR skin).

2 = Moderate (redness of most or all lid margin OR skin).

3 = Severe (redness of most or all lid margin AND skin).

4 = Very severe (marked diffuse redness of both lid margin AND skin).

Lid - Oedema

0 = None (normal).

1 = Mild (localised to a small region of the lid).

2 = Moderate (diffuse, most or all lid but not prominent/protruding).

3 = Severe (diffuse, most or all lid AND prominent/protruding).

4 = Very severe (diffuse AND prominent/protruding AND reversion of the lid).

Lashes

0 = Normal

1 = Abnormal (specify)

Conjunctiva – Erythema

0 = None (normal).

1 = Mild (a flush reddish colour predominantly confined to the palpebral or bulbar conjunctiva).

2 = Moderate (more prominent red colour of the palpebral or bulbar conjunctiva).

3 = Severe (definite redness of palpebral or bulbar conjunctiva).

Conjunctiva - Oedema

0 = None (normal).

1 = Mild (slight localised swelling).

2 = Moderate (moderate/medium localised swelling or mild diffuse swelling).

3 = Severe (severe diffuse swelling).

4 = Very severe (very prominent/protruding diffuse swelling).

Tear Film Debris

0 = None (absence of debris).

1 = Mild (presence of debris in inferior tear meniscus).

2 = Moderate (presence of debris in inferior tear meniscus and in tear film overlying cornea).

3 = Severe (presence of debris in inferior tear meniscus and in tear film overlying cornea. Presence of mucus strands in inferior fornix of on bulbar conjunctiva).

4 = Very severe (presence of debris in inferior tear meniscus and in tear film overlying cornea. Presence of numerous AND/OR adherent mucus strands in inferior fornix and on bulbar conjunctiva or filamentary keratitis).

Anterior Chamber Inflammation

0 = None (no Tyndall effect).

1 = Mild (Tyndall effect barely discernible).

2 = Moderate (Tyndall beam in the anterior chamber is moderately intense).

3 = Severe (Tyndall beam in the anterior chamber is severely intense).

Lens

0 = No opacification (normal lens).

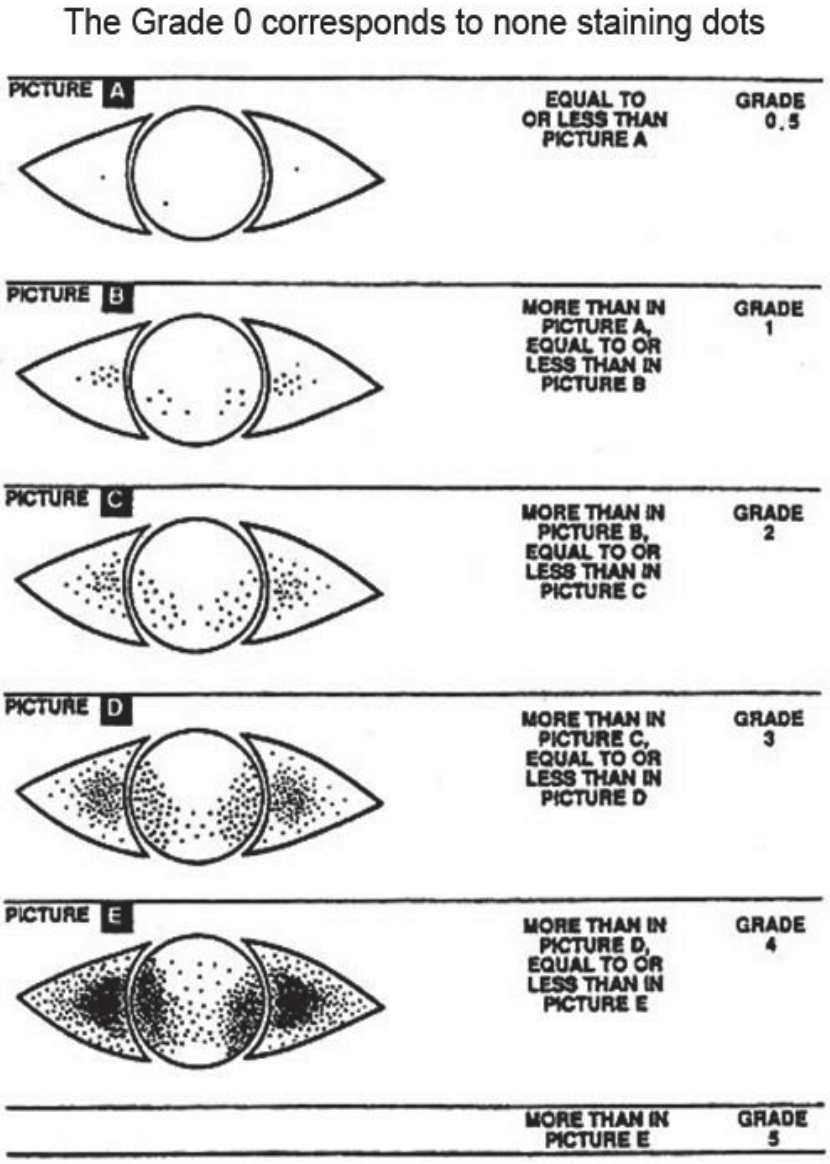
1 = Mild lens opacification.

2 = Moderate lens opacification.

3 = Severe lens opacification.

Appendix A-IV Modified Oxford Scale

(Grading of corneal and conjunctival fluorescein staining)



Appendix A-V Dry Eye related Quality of life Score (DEQS)

The DEQS is self-administered and should be completed by the patient.

This questionnaire asks about how much you experience various eye symptoms, and also what kind of problems you experience in your daily life. Your answers will be used to inform future medical care. Please do not think too hard about the questions; just answer based on what you feel.

◇ **For each question below, circle one response from 0-4 in Column A.**
- ➢ **If your answer is 0 ("Never") in Column A ➜ Move onto the next question.**
- ➢ **If your answer is 1-4 in Column A ➜ Also circle one from 1-4 in Column B.**

Please answer <u>all</u> questions without missing any.

◆ <u>During the past 7 days,</u> did you experience the following symptoms?	Column A						Column B			
	Never	Occasionally	Sometimes	Often	Always		Hardly bothered me	Bothered me a little	Bothered me	Bothered me very much
1) Grittiness (sensation of something in your eye)	0	1	2	3	4	➜	1	2	3	4
2) Dry eyes	0	1	2	3	4	➜	1	2	3	4
3) Sore eyes	0	1	2	3	4	➜	1	2	3	4
4) Tired eyes	0	1	2	3	4	➜	1	2	3	4
5) Heavy eyelids	0	1	2	3	4	➜	1	2	3	4
6) Red eyes	0	1	2	3	4	➜	1	2	3	4

Go to the next questions ↗

- If your answer is 0 ("Never") in Column A ➔ Move onto the next question.
- If your answer is 1-4 in Column A ➔ Also circle one from 1-4 in Column B.

◆ During the past 7 days, did you experience the following?	Column A						Column B			
	Never	Occasionally	Sometimes	Often	Always		Hardly bothered me	Bothered me a little	Bothered me	Bothered me very much
7) Difficulty keeping my eyes open (due to my symptoms)	0	1	2	3	4	➔	1	2	3	4
8) Vision became blurry when engaging in activities that required sustained visual attention (e.g. computer working, reading, knitting, etc.)	0	1	2	3	4	➔	1	2	3	4
9) Light was too bright	0	1	2	3	4	➔	1	2	3	4
10) Eye symptoms worsened when reading newspapers, magazines or books	0	1	2	3	4	➔	1	2	3	4
11) Eye symptoms worsened when watching TV or when using a computer/mobile phone	0	1	2	3	4	➔	1	2	3	4
12) Eye symptoms reduced my ability to concentrate	0	1	2	3	4	➔	1	2	3	4
13) Eye symptoms interfered with work, housework or studying	0	1	2	3	4	➔	1	2	3	4
14) Tended to avoid leaving the house because of eye symptoms	0	1	2	3	4	➔	1	2	3	4
15) Felt down due to eye symptoms	0	1	2	3	4	➔	1	2	3	4

◇ Finally, please tell us how you have been overall for the past week, including your eye symptoms and how they have affected your daily life.
From the responses below, please circle the number that best describes your condition.

1	2	3	4	5	6
Extremely good	Very good	Good	Bad	Very bad	Extremely bad

Thank you for completing the questionnaire.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are patient to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarised in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non-standard panel) eligibility assessments are NOT performed on potential patients, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C 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.
- 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.

Appendix D 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 E 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.