Statistical Analysis Plan Cover Page

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

FAST / NVG16E128

Protocol Title:	A Phase IV, Prospective, Open-Label, Multicentre, Single Arm, 3-Month Proof Of Concept Study To Assess The Effect Of IKERVIS® 1 mg/mL (Ciclosporin) Eye Drops Administered Once Daily On The Quality Of Vision In Dry Eye Disease (DED) Patients With Severe Keratitis
Product:	IKERVIS® Eye Drops (1 mg/mL Ciclosporin)
Protocol Number:	NVG16E128
Sponsor:	Santen SAS Genavenir IV, 1 rue Pierre Fontaine F-91058 Evry, France
Date:	19-February-2019
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CONFIDENTIAL

APPROVAL SIGN-OFF SHEET

A Phase IV, Prospective, Open-Label, Multicentre, Single Arm, 3-Month Proof Of Concept Study To Assess The Effect Of IKERVIS® 1 mg/mL (Ciclosporin) Eye Drops Administered Once Daily On The Quality Of Vision In Dry Eye Disease (DED) Patients With Severe Keratitis

IKERVIS® FAST / NVG16E128

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ABBREVIATIONS

AE	Adverse Event
AR(1)	Autoregressive (covariance structure)
ARH(1)	Heterogeneous Autoregressive (covariance structure)
AT	Artificial tears
ATC	Anatomical-Therapeutic-Chemical
BCDVA	Best-Corrected Distance Visual Acuity
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
CRO	Contract Research Organization
CS	Compound Symmetry (covariance structure)
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
DED	Dry Eye Disease
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVA	Functional Visual Acuity
HOA	Higher-Order Aberrations
IOP	Intraocular Pressure
LOCF	Last-Observation-Carried-Forward
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mg/mL	Milligram per milliliter
mmHg	Millimeter of mercury
OSI	Objective Scatter Index
PP	Per-Protocol
RMS	Root Mean Square
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAS	Statistical Analysis System
SOC	System Organ Classification
TBUT	Tear Break Up Time
TEAE	Treatment-Emergent Adverse Event
TOEP	Toeplitz (covariance structure)
TOEPH	Heterogeneous Toeplitz (covariance structure)
UDVA	Uncorrected Distance Visual Acuity
UN	Unstructured (covariance structure)
VA	Visual Acuity
VAS	Visual Analog Scale
VC	Variance Components (covariance structure)
VMR	Visual Maintenance Ratio
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected from the FAST study within the scope of Santen's Protocol NVE16E128, "A Phase IV, Prospective, Open-Label, Multicentre, Single Arm, 3-Month Proof Of Concept Study To Assess The Effect Of IKERVIS® 1 mg/mL (Ciclosporin) Eye Drops Administered Once Daily On The Quality Of Vision In Dry Eye Disease (DED) Patients With Severe Keratitis". It applies to the Amendment 1 of the study protocol, dated 07 April 2017 (version 3.0) and provides detailed instructions as to how each analysis will be performed.

Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report (CSR) for this protocol. Any deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the CSR.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The secondary objectives are:

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

2.2 Endpoints

Efficacy endpoint-related definitions are provided in Section 4.3.

2.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

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

2.2.2 Secondary Endpoints

2.2.2.1 Efficacy Endpoints

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

2.2.2.2 Safety Evaluations

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

3 STUDY DESIGN

3.1 General Study Design

The proposed 3-month study is a prospective, open-label, multi-center, phase IV, proof-of-concept study. The study is designed to assess the effect on the quality of vision of IKERVIS® (1 mg/mL ciclosporin) eye drops administered once daily in dry eye disease (DED) patients with severe keratitis, as well as its safety and efficacy. Thirty-three adult patients are planned to be enrolled in the study in order to obtain 30 completed patients. However, due to the much slower than expected enrollment and budget constraint, this study enrolled 17 patients.

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

At the Baseline Visit (Day 1) following the 2-week wash-out phase, patients who meet the inclusion criteria for DED and severe keratitis will start the treatment phase with the study treatment (IKERVIS® 1mg/mL). Patients not fulfilling the inclusion criteria or meeting any of the exclusion criteria following the wash-out phase will exit the study without receiving any study medication.

Major inclusion criteria for the eligible eye are DED patients with persistent severe keratitis at the Screening and Baseline Visits defined as the following:

- CFS score of 3, 4 or 5 on the modified Oxford scale, AND
- Visual Maintenance Ratio (VMR) < 0.95, AND
- OSI ≥ 2, AND
- Variance of OSI ≥ 0.5.

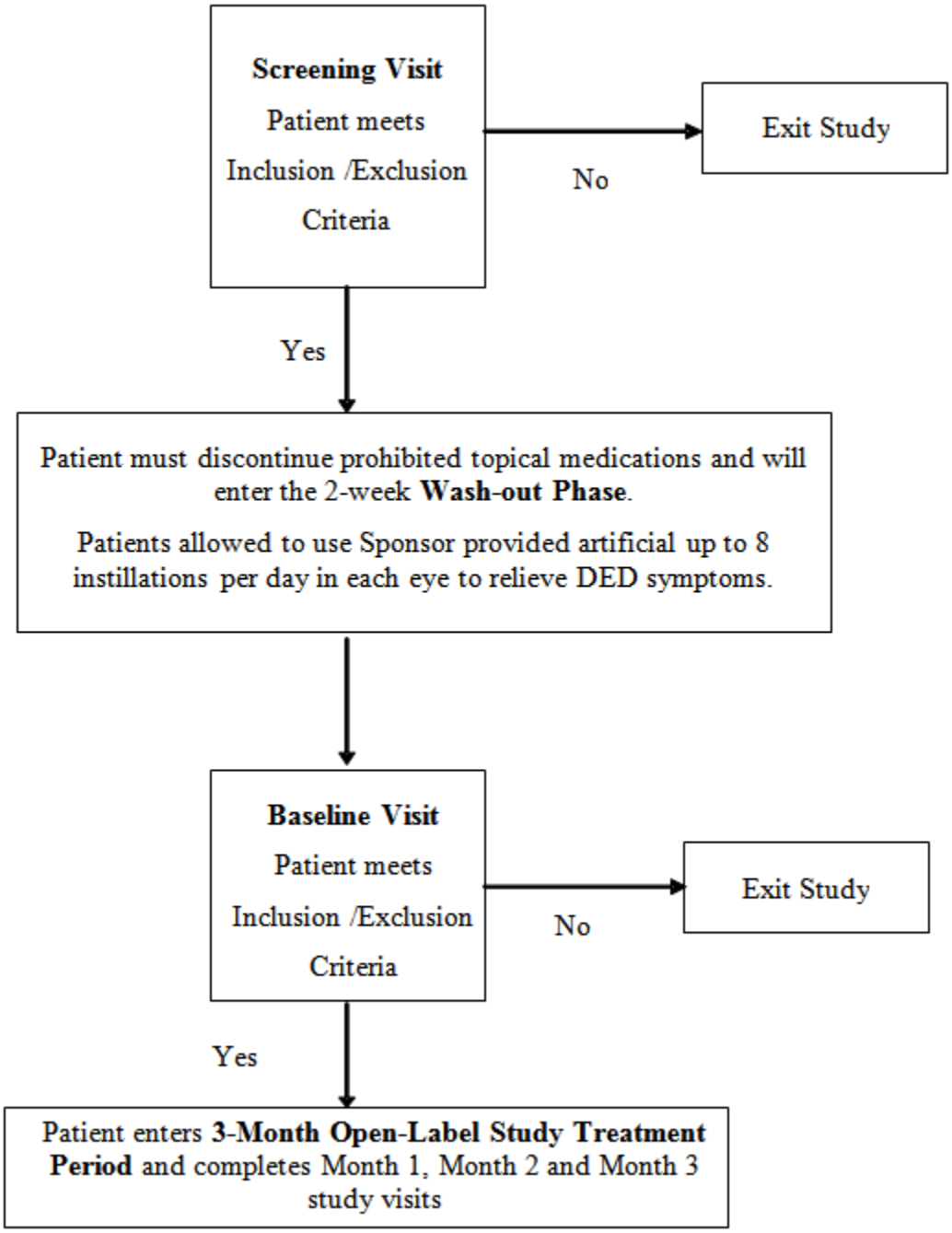
During the Baseline Visit, patients will be instructed to instill one drop of study medication (IKERVIS® 1mg/mL) once daily in each eye at bedtime and will be scheduled for three additional study visits, Month 1 (Day 28 ±3), Month 2 (Day 56±3), and Month 3 (Day 84±7). In addition to the study medication,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

The study flowchart is illustrated in Figure 1.

3.2 Randomization and Masking

This is a single-arm, open-label study, no randomization and masking will be applied.

Figure 1 Study Flow Chart



3.3 Sample Size Planning

A total of 33 subjects was planned to be enrolled to obtain 30 completed subjects in this study. The sample size for this proof-of-concept study was not calculated based on statistical considerations. Clinical judgment and experience were the basis for determining the number of subjects needed to achieve study goals.

3.4 Visits and Assessments

The study period will include the initial Screening Visit, the 2-week wash-out phase, and the 3-month open-label study treatment phase encompassing the Baseline, Month 1, Month 2 and Month 3 study visits. The schedule for all study-related procedures for all evaluations is shown in Table 1.

Table 1 Schedule of Study Procedures

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

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

ET/EOT=early termination/end of treatment.

1 VASs should be performed at the beginning of the visit before medical history and any study assessment.

2 Dispense unpreserved artificial tears. Instruction: to be instilled up to eight times per day in each eye

3 Only for patients fulfilling criteria for severe keratitis that will be included.

4 Assessments to be performed during unscheduled visits only in case of premature discontinuation

4 DEFINITIONS

4.1 Time-Related Terms

4.1.1 Screening Visit (Day -14 ± 3 days)

The *Screening Visit* is the visit when the subject will be screened in accordance with the protocol-defined inclusion and exclusion criteria. It will be performed within 14 days prior to the first dose of the study medication administration.

4.1.2 Baseline Visit (Day 1)

The *Baseline Visit* is the Day 1 visit when the subject will receive the first dose of the study medication.

4.1.3 Analysis Period and Treatment Start and End Dates

There will be only one analysis period for this study:

Analysis Period	Analysis Period Start Date	Analysis Period End Date
Open-label treatment period	The date of the first dose of the study medication administration	The Study Exit date

4.1.4 Study Day

The *study day* describes the relative day of an observation starting with the reference date. For this study, the treatment start date is the reference date and the *study day* will be calculated as:

- For days prior to the treatment start date, Study Day = Date – Treatment Start Date
- For days on/after the treatment start date, Study Day = Date – Treatment Start Date + 1

Note that there is no Study Day 0.

4.1.5 Out-of-Window Measurements, Analysis Visit, and Analysis Window

For this study, a measurement collected at a visit is an *out-of-window* measurement if the study day of the visit falls outside of a visit window specified in Assessment Schedule (Table 1; otherwise, it will be treated as a *within-window* measurement.

Analysis visit is a timing variable to be used for analyses involving visits. For each analysis visit, an analysis window is set up to determine the analysis visit to which a measurement should be mapped. The *analysis window*, which is wider than the visit window, will be employed to minimize the amount of missing data for analysis purposes.

Post-baseline Visit (Target Assessment Date)	Visit Window	Analysis Window
Month 1 (Day 28)	[25, 31]	[21, 48]
Month 2 (Day 56)	[53, 59]	[49, 76]
Month 3 (Day 84)	[77, 91]	[77, 104]

The analysis visit of a measurement will be determined based on the study day of the measurement and specified analysis windows, and it is not necessarily the same as the study visit at which the measurement was collected. For example, an out-of-window measurement collected at the Month 2 study visit will be mapped to the Month 3 analysis visit, if the study day of the measurement falls into the analysis window of Month 3.

For analyses involving post-baseline visits, if there are two or more measurements that fall into the same analysis window of a post-baseline visit, then the measurement closest to the target assessment day will be selected for that visit. In the case that two measurements are closest and equidistant to the target assessment day, i.e., one is before and one is after the target assessment day, the later one will be selected for that visit.

4.1.6 Extent of Exposure

The *extent of exposure* to study medication will be assessed by duration of treatment exposure, which will be derived using the following formula:

Duration of treatment exposure = (Treatment end date – Treatment start date) + 1

4.1.7 Duration of Quitting Smoke

For ex-smokers, the *duration of quitting smoke* will be derived using the following formula:

Duration of quitting smoke = (Date of Screening Visit – Smoking stop date) + 1

4.2 Endpoint-Related Definitions

4.2.1 Analysis Eye and Fellow Eye

The *analysis eye* of an enrolled subject is defined as the eligible eye, the eye that fulfills all the criteria listed under the inclusion criteria #4. If both eyes are eligible, the eye with the highest baseline CFS score will be chosen. If both eyes have the same CFS score, the eye with the lowest baseline VMR will be chosen. If VMR values are the same for both eyes, the right eye will be chosen. The *fellow eye* is the non-analysis eye.

4.2.2 Baseline Score

For any measure, the *baseline score* is the last observed measurement prior to the first dose of the study medication. If any variable is missing a value on Day 1, values from the Screening

Visit will be used to impute the baseline score, i.e., the last observation carried forward (LOCF) approach will be used.

4.2.3 Change from Baseline

The change from baseline in a measure at a post-baseline visit will be derived as:

Change = (Score at the Post-Baseline Visit) – (Baseline Score)

4.3 Efficacy-Related Definitions

4.3.1 Functional Visual Acuity (FVA) Parameters

Functional Visual Acuity (FVA) parameters will be obtained from the FVA measurement system at each scheduled visit and at the premature study discontinuation visit. FVA parameters assess dynamic visual acuity over a period of 60 seconds. Measurements will be made under natural blinking conditions without topical anesthesia.

FVA parameters include:

- **FVA**: FVA is the mean value of time-wise change of visual acuity measured using the FVA measurement system during the overall examination period (60 seconds). It is measured under the natural blinking state without topical anaesthesia and expressed in decimal notation.
- **LogMAR FVA**: LogMAR FVA is FVA converted to LogMAR notation. LogMAR FVA will be the variable used for all the analyses (instead of FVA). A decrease from baseline in LogMAR FVA indicates improvement.
- **Visual Maintenance Ratio (VMR)**: VMR is an objective index for evaluating changes of dynamic vision from baseline visual acuity. It is defined as the ratio of LogMAR FVA over the 60 seconds divided by the value of Starting LogMAR VA. An increase from baseline in VMR indicates improvement.
- **Starting VA and Starting LogMAR VA**: Starting VA is the baseline visual acuity for a 60-second examination period; it is the value of the best corrected visual acuity measured by the FVA measurement system at the beginning of the 60-second examination period. Starting LogMAR VA is Starting VA converted to LogMAR notation.
- **Minimal VA and Minimal LogMAR VA**: Minimal VA is the lowest visual acuity recorded during the 60-second examination period. Minimal LogMAR VA is Minimal VA converted to LogMAR notation.
- **Maximal VA and Maximal LogMAR VA**: Maximal VA is the highest visual acuity recorded during the 60-second examination period. Maximal LogMAR VA is Maximal VA converted to LogMAR notation.

4.3.2 Objective Scatter Index (OSI)

OSI and its variance will be measured using a double-pass aberrometer at each scheduled visit and at the premature study discontinuation visit. OSI is an objective way to assess the intensity of the subjective visual disturbances.

A decrease from baseline in OSI or its variance indicates improvement.

4.3.3 Corneal Fluorescein Staining (CFS) including Complete Corneal Clearing

CFS will be used to assess corneal damage and will be measured at each scheduled visit and at the premature study discontinuation visit. It will be graded using the modified Oxford scale, which is a 7-point ordinal scale in which a score of 0 represents no staining dot, and scores of 0.5, 1, 2, 3, 4, or 5 represent increased numbers of staining dots, corresponding to increased severity of corneal damage. A CFS grade of 0 represents complete corneal clearing.

A decrease from baseline in CFS indicates improvement.

4.3.4 Higher-Order Aberrations (HOA)

At the Screening Visit and Month 3/premature study discontinuation visit, serial measurements of ocular higher-order aberrations (HOA) are performed by means of the Hartmann-Shack wavefront aberrometer. HOA will be measured during a blink-free period of 20 seconds without instillation of topical anaesthesia. Because HOA data will not be collected at the Baseline Visit (Day 1), data collected from the Screening Visit will be used as the baseline measures in change from baseline analyses.

The following HOA parameters will be collected:

- **Root mean square (RMS)**: RMS is calculated from the Zernike coefficients to represent the wavefront aberrations. A decrease from baseline in RMS indicates improvement.
- **Coma-like aberrations (S3)**: S3 is the RMS of the third-order Zernike coefficients.
- **Spherical-like aberrations (S4)**: S4 is the RMS of the fourth-order Zernike coefficients.
- **Total higher-order aberrations (S3 + S4)**: S3 + S4 is the sum of the third-order and fourth-order Zernike coefficients.

4.3.5 Symptoms Measured on Visual Analogue Scales (VAS)

Patient's photophobia and blurred vision will be assessed on each eye, separately, at each scheduled visit and at the premature study discontinuation visit using a visual analogue scale (VAS). The VAS ranges from 0% to 100%; 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort".

A decrease from baseline in the VAS indicates improvement.

4.3.6 Tear Break-Up Time (TBUT)

Tear break-up time (TBUT) will be measured by determining the time to tear break-up at each scheduled visit and at the premature study discontinuation visit. At each visit, the TBUT will be measured twice. If the 2 readings differ by more than 2 seconds, a third reading will be taken. This measurement will be performed with 10 seconds maximum. The TBUT value will be the average of the 2 or 3 measurements. A measured value of less than 10 seconds will be recorded; a measured value of 10 seconds or greater will be recorded as 10 seconds.

An increase from baseline in TBUT indicates improvement.

4.3.7 Schirmer Test (without Anaesthesia)

At the Baseline Visit (Day 1) and Month 3/premature study discontinuation visit, Schirmer test will be performed without anaesthesia to record the length of the tear absorption on the strip in 5 minutes. It will be recorded as mm wetting/5 min.

An increase from baseline in Schirmer test indicates improvement.

4.3.8 Patient Global Evaluation of Efficacy

At the Month 3/premature study discontinuation visit, patients will provide an overall assessment of the effect of the study medication using the following rating scale:

(3) = Very satisfactory

(2) = Satisfactory

(1) = Not very satisfactory

(0) = Unsatisfactory.

4.3.9 Investigator Global Evaluation of Efficacy

At the Month 3/premature study discontinuation visit, the study investigator will provide an overall assessment of the effect of the study medication on the improvement of that patient's DED using the following rating scale:

(3) = Very satisfactory

(2) = Satisfactory

(1) = Not very satisfactory

(0) = Unsatisfactory.

4.3.10 Use of Concomitant Artificial Tears

The use of artificial tears (AT) will be monitored over the course of the study for each patient. At each scheduled visit and at the premature study discontinuation visit, patients will be asked about the average number of times per day artificial tears were used the week preceding the visits, and

the number of days they were not used during the week preceding the visits. Patients will be allowed to instill 1 unpreserved artificial tear drop, up to eight instillations per day in each eye, to ameliorate their dry eye symptoms. Artificial tear usage in the past 7 days will be derived using the following equation:

AT usage = Average number of times per day used AT × (7 – number of days without AT use)

A decrease from baseline in the AT usage indicates improvement.

4.4 Safety-Related Definitions

4.4.1 Adverse Event (AE)

Events reported on the AE electronic case report form (eCRF) will be assessed according to the amended FDA regulations 21 CFR Parts 312 and 320.

Under Protocol NVG16E128, an AE is defined as any untoward medical occurrence in a clinical investigation patient administered an investigational product; it does not necessarily have to have a causal relationship with the treatment. An AE will be considered as a *pre-treatment event* (PTE) if the AE occurred after the patient has signed informed consent to participate in the study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation. An AE will be considered as *treatment-emergent* if the AE occurred on or after the treatment start date up to the last study visit or worsened relative to pre-treatment state.

The severity of each AE will be graded by the Clinical Investigator as Mild (aware or unaware of event, but easily tolerated), Moderate (discomfort enough to cause interference with usual activity), or Severe (incapacitating; unable to work or perform usual activity). AEs will also be rated by the Investigator as to their causality/relationship to the study medication, to the Sponsor provided artificial tears, as well as to the study procedures (related vs. not related).

Each AE will be classified into a system organ classification (SOC) and coded to a preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA, version v19.1 English, March 2016).

4.4.1.1 Serious Adverse Event (SAE)

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

1. Results in DEATH.
2. Is LIFE THREATENING.

   The term “life threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.

5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the patient to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
7. Sight-threatening events.

PTEs that fulfill 1 or more of the serious criteria above will also be considered as SAEs and should be reported and followed up in the same manner.

4.4.1.2 Sight-Threatening Adverse Event

The *sight-threatening AE* is defined as any serious ocular AE that places the subject at immediate risk of permanent vision loss in either the analysis eye or the fellow eye. In this study, the following serious ocular AEs will be reported as sight-threatening AEs if it meets one or more of the following criteria:

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

4.4.1.3 Case of Special Interest

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

- Overdose:

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

- Misuse of study product:

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

- Medication error:

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

- Abuse of study product:

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

4.4.1.4 Adverse Event Leading to Discontinuation

An AE will be counted as an *AE leading to Discontinuation* if the Investigator selected "AEs" in the "Primary reason for discontinuation or withdrawal" checklist on the END OF STUDY eCRF and checked "Definitive discontinuation" in the "Action taken regarding study drug" checklist on the AE eCRF.

4.4.1.5 Ocular Adverse Events

An AE will be counted as an *ocular AE* if the Clinical Investigator selected "Right Eye" or "Left Eye" or "Both Eyes" under the "Location" on the AE eCRF.

4.4.1.6 Systemic Adverse Events

An AE will be counted as a *systemic AE* if the Clinical Investigator selected "Other" or with a missing value under the "Location" on the AE eCRF.

4.4.2 Other Safety Evaluation Parameters

4.4.2.1 Slit Lamp Examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp at each scheduled visit. Grading of the Meibomian glands, conjunctival erythema, anterior chamber inflammation, lens, and vitreous will be on a 0 to 3 scale; 0 indicates normal and 3 indicates the most severe state. Lid erythema, lid oedema, conjunctival oedema, and tear film debris will be graded on a 0 to 4 scale; 0 indicates normal and 4 indicates the most severe state. Lashes will be graded as normal or abnormal (Appendix A).

A decrease in slit lamp grading indicates an improvement in the slit lamp finding.

4.4.2.2 Uncorrected Distance Visual Acuity (UDVA)

UDVA will be measured on LogMAR scale at each scheduled visit and at the premature study discontinuation visit.

A decrease in LogMAR UDVA indicates improvement in the uncorrected distance visual acuity.

4.4.2.3 Best-Corrected Distance Visual Acuity (BCDVA)

BCDVA measures the acuteness or clearness of best-corrected distance vision. It will be measured on LogMAR scale at each scheduled visit and at the premature study discontinuation visit.

A decrease in LogMAR BCDVA indicates improvement in the best-corrected distance visual acuity.

4.4.2.4 Dilated Fundus Examination

A dilated fundus examination will be performed after the pupil is dilated at the Baseline and Month 3/early termination visits in order to evaluate for posterior segment diseases. It will be rated as normal or abnormal.

4.4.2.5 Intraocular Pressure (IOP)

IOP will be measured using Goldman applanation tonometry (one measurement) at the Baseline and Month 3/early termination visits.

A decrease in IOP indicates improvement in the intraocular pressure.

4.5 Other Definitions

4.5.1 Prior and Concomitant Medications

Non-study medications will be categorized into prior medications and concomitant medications. Specifically, *prior medication* is defined as any non-study medication taken and ended prior to the treatment start date. *Concomitant medication* is defined as any non-study medication taken concurrently while on the study medication.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE), Format C English, March 2016. Each prior or concomitant medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO-DDE preferred drug name.

4.5.2 Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent.

4.5.3 Treatment Compliance

Compliance to the study medication use is tracked on the Compliance eCRF as the number of single dose medication containers dispensed at the beginning of the study period plus the number of single dose containers dispensed at any unscheduled visit during that period, and the number of used and unused containers returned or not returned at the following visit (including unscheduled visits). For the purpose of treatment compliance calculation, there will be three study periods:

- Baseline Visit (Day 1) to Month 1 Visit
- Month 1 Visit to Month 2 Visit
- Month 2 Visit to Month 3 Visit

For a given study period, compliance rate is calculated using the following formula, which assumes that the unreturned bottles are not used:

$$\text{Compliance} = \frac{\text{Number of containers used}}{\text{Number of days of the follow-up interval}} \text{ x } 100$$

$$= \frac{\text{Number of USED containers returned}}{\text{Date of current visit} - \text{Date of preceding visit}} \text{ x } 100$$

Compliance rate of ≥ 80% will be treated as compliant.

For subjects who did not return their used and/or unused bottles at the next visit, that patient will be treated as 100% compliant if the site could confirm that the patient was compliant during the preceding month.

5 STUDY POPULATION

5.1 Full Analysis Set

The *Full Analysis Set* (FAS) includes all enrolled subjects who received at least one dose of the study medication. This will be the population used for efficacy analyses.

5.2 Safety Population

The *Safety* population will include all enrolled subjects 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.

5.3 Per-Protocol Population

The *Per-Protocol* (PP) population will be a subset of the FAS subjects. It includes all FAS subjects without any of the following protocol deviations that could affect the primary efficacy endpoint.

- Failing to fulfill certain inclusion/exclusion criterion(a)
- Has a significant protocol deviation that could alter his/her efficacy outcome to treatment
- Without the primary efficacy measures of CFS, VMR, and OSI at the Month 3 visit
- Other significant protocol deviations identified by Santen's study team

Santen's study team will review all protocol deviations and identify subjects to be excluded from the PP population before the database lock.

6 GENERAL CONSIDERATIONS

Statistical analyses will be performed based on this SAP by the Biometry Unit of Euraxi, a contract research organization (CRO) based in Joué Les Tours, France.

Unless specified otherwise, all efficacy analyses will be performed using data from the analysis eye of FAS subjects, and all safety variables will be analyzed separately for both the analysis eyes and the fellow eyes on the Safety population.

Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

All statistical testing will be conducted at a significance level of 0.05 (two-sided) unless specified otherwise. No statistical testing will be conducted for safety measures.

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

6.1 Adjustments for Covariates

Details on covariates to be included in the statistical model for each individual statistical analysis are provided in Section 8.1.2.

6.2 Handling of Missing Data

6.2.1 Efficacy Endpoints

Missing observations on CFS, VMR, and variance of OSI will be imputed by the last-observation-carried-forward (LOCF) approach.

6.2.2 Safety Endpoints

Descriptive summaries of safety measures will be based on observed data only. No imputation of missing scores will be implemented.

6.2.3 Dates for Medical Events and Medications

Completely or partially missing onset and/or resolution dates for medical events (including AEs, medical history, and concomitant medications) will be imputed in a conservative fashion as follows:

Date	Type of Missing Date	Handling of Missing Date
Event onset date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied.
	Only YYYY is available	Use the first day of YYYY to impute the missing month and date parts of the onset date

	YYYY and MM are available but DD is missing	Use the first day of MM to impute the missing date part of the onset date
Event resolution date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the last visit date.
	Only YYYY is available	Use the last day of YYYY to impute the missing month and date parts of the resolution date
	YYYY and MM are available but DD is missing	Use the last day of MM to impute the missing date part of the resolution date

6.3 Multi-Center Studies

This is a multi-center study enrolling subjects from approximately 4 France centers. Sites will not be pooled into any subgroups for any inferential analysis. Sites will be included as a covariate in the mixed-effects model for repeated measures (MMRM) analysis.

6.4 Multiple Comparisons / Multiplicity

Since the FAST study is a proof-of-concert study and considered as purely exploratory, no multiplicity adjustment will be conducted to control the overall Type I error rate.

6.5 Interim Analysis

No formal interim analysis is planned for this study.

7 SUMMARY OF STUDY POPULATION DATA

7.1 Subject Disposition

The subject disposition for all enrolled subjects will be tabulated by study population and completion status at Month 3. Subjects who discontinued the study before Month 3 will be tabulated by the primary discontinuation reason. In addition, the subject enrollment will be summarized by site.

7.2 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for all FAS subjects. Specifically, for subject demographics, the following variables will be summarized:

- Age at enrollment (continuous and categorical: < 65 years, ≥ 65 years)
- Gender (male, female)
- For female patients, contraception and pregnancy avoidance procedure (confirmed menopause, effective contraception, none)

For baseline characteristics, the following variables will be summarized:

- Alcohol use [≤ 30 g per day (women) or ≤ 40 g per day (men), > 30 g per day (women) or > 40 g per day (men)]
- Illicit or recreational drug use (yes, no)
- Tobacco use
    - Yes
        - Ex-smoker (number of packets per year, duration of smoking, duration of quitting smoke)
        - Current smoker (number of packets per year, duration of smoking)
    - No
        - Passive tobacco use (yes, no)

7.3 Medical and Surgical History

The medical and surgical history (i.e., medical events) will be coded using MedDRA (version v19.1 English, March 2016) and summarized for the FAS population. Each medical event will be classified into a system organ class (SOC) and mapped to a preferred term (PT). Any subject with more than one medical and/or surgical term within the same SOC or mapped to the same PT will be counted only once for that SOC or PT.

7.4 Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Safety issues
    - Study drug storage condition outside of the protocol-defined condition

- Consent issues
    - Informed consent not signed
    - Informed consent data missing or not available
- Enrollment issues
    - Ineligible subject enrolled
- Protocol implementation issues
    - Visit out of window
    - Protocol-required exam(s) not done or missing
    - Administered rescue medication/therapy
    - Used prohibited medications/therapy
    - Non-compliance (compliance rate < 80%)
- Other

A protocol deviation is considered major if it may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Santen's study team will review all protocol deviations and determine the list of major protocol deviations prior to database lock. FAS subjects with any major protocol deviation(s) will be tabulated by deviation category. In addition, protocol deviation(s) will also be listed.

7.5 Prior and Concomitant Medications

All prior and concomitant medications will be coded using WHO-DDE (Format C English, March 2016) on the FAS subjects and summarized separately. Each prior or concomitant medication will be classified using the ATC classification system and mapped to a WHO-DDE preferred drug name. A subject will be counted at most once for each prior or concomitant medication, respectively, even if the subject took the same prior or concomitant medication on multiple occasions.

7.6 Treatment Compliance

Treatment compliance will be calculated as described in Section 4.5.3. Compliance rate for FAS subjects will be summarized by study period (Day 1 – Month 1, Month 1 – Month 2, and Month 2 – Month 3).

7.7 Treatment Exposure

Treatment exposure to the study medication is measured by days on treatment as derived in Section 4.1.6. Subjects in the Safety Population will be tabulated by duration category (0-30, 31-60, 61-90, and > 90 days).

7.8 Pregnancy During the Course of the Study

Urine pregnancy test will be performed on all women of childbearing potential at the Screening, Baseline (Day 1), Month 3 or early termination visits. For subjects who become pregnant during the course of the study, their positive testing results will be provided in a listing.

8 EFFICACY ANALYSES

Unless specified otherwise, all efficacy analyses will be performed on the analysis eye of the FAS population.

For each efficacy measure listed in Section 4.3, correlation coefficients, scores and change-from-baseline scores will be summarized descriptively by analysis visit. There will be no formal hypothesis testing because this is a single-arm, open-label study.

8.1 Analyses of Primary Efficacy Endpoints

The primary efficacy endpoints are:

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

8.1.1 Primary Analyses of the Primary Endpoints

Spearman's coefficient of correlation and its 95% confidence interval will be calculated at Month 3 between the change from baseline of CFS and, respectively, the change from baseline of VRM and the change from baseline of variance of OSI.

8.1.2 Sensitivity Analyses of the Primary Endpoints

The following sensitivity analyses will be performed on the primary efficacy endpoints:

- Correlation between the change from baseline in VMR or variance of OSI, respectively, and the change from baseline in the CFS will be analyzed using a mixed-effects model for repeated measures (MMRM) on observed cases collected up to Month 3 (Laird & Ware, 1982; Lindstrom & Bates, 1988). No imputation of missing data will be needed. Change from baseline in CFS will be used as the predictor variable, and VMR or variance in OSI will be treated as the dependent variable. Baseline CFS will be included as a covariate and subjects as a random effect.

  An unstructured (UN) covariance matrix will be used to model the within-subject errors. If the UN model fails to converge, then a heterogeneous Toeplitz (TOEPH) covariance matrix will be used to model the within-subject errors. If the TOEPH model fails to converge, then the heterogeneous first-order auto-regressive [ARH(1)] model will be used. If ARH(1) model also fails to converge, then the Toeplitz (TOEP) model, the first-order auto-regression [AR(1)] model, the compound symmetry (CS) model, and the variance components (VC) model will be fitted sequentially until the convergence criteria are met.
- The primary analyses will be repeated with the PP population.
- The primary analyses will be repeated with the observed data only.

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

8.2 Analyses of Secondary Efficacy Endpoints

8.2.1 Analyses of Continuous Secondary Efficacy Endpoints

The following continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, coefficient of variation, median, minimum, and maximum by analysis visit.

- CFS scores assessed at each visit with the Modified Oxford Scale and change from baseline at Months 1, 2 and 3.
- FVA parameters (VMR, LogMAR FVA, starting visual acuity, and minimal and maximal VAs) assessed at each visit and their change from baseline at Months 1, 2 and 3.
- OSI and its variance assessed at each visit and their change from baseline at Months 1, 2 and 3.
- Root mean square (RMS) of higher order aberrations (total, coma-like, spherical like) measured with Hartmann-Schack aberrometer at each visit and their change from baseline at Month 3.
- Tear break up time (TBUT) assessed at each visit and change from baseline at Months 1, 2 and 3.
- VAS scores (photophobia, blurred vision) assessed at each visit and their change from baseline at Months 1, 2 and 3.
- Artificial tear usage assessed at each visit and change from baseline at Months 1, 2 and 3.

8.2.2 Analyses of Categorical Secondary Efficacy Endpoints

The following categorical variables will be tabulated using frequency (n) and percent (%).

- CFS scores assessed at each visit will also be summarized categorically.
- Shift from baseline in CFS scores at Months 1, 2, and 3.
- Patient global evaluation of efficacy at Month 3/early termination visit.
- Investigator global evaluation of efficacy at Month 3/early termination visit.

8.2.3 Correlation Analyses

8.2.3.1 Correlation Analyses for Data Collected from the Same Visits

Spearman's coefficients of correlation and its 95% confidence interval will be calculated at each follow-up visit between the change from baseline of the following pairs of variables (Month 1 vs. Month 1, Month 2 vs. Month 2, and Month 3 or Month 3, respectively):

- Change from baseline in **CFS** vs. the change from baseline of following variables, respectively:
    - FVA parameters
        - VMR
        - LogMAR FVA
        - Starting visual acuity (LogMAR scale)
        - Minimal visual acuity (LogMAR scale)
        - Maximal visual acuity (LogMAR scale)
    - OSI parameters
        - OSI
        - Variance of OSI
    - VAS symptom scores
        - Blurred vision
        - Photophobia
    - TBUT
    - Schirmer's test
    - HOA RMS
    - Visual acuity
        - BCDVA (logMAR)
        - UDVA (logMAR)

- Change from baseline in **FVA (logMAR)** vs. the change from baseline of following variables, respectively:
    - OSI parameters
        - OSI
        - Variance of OSI
    - VAS symptom scores
        - Blurred vision
        - Photophobia
    - TBUT
    - Schirmer's test
    - HOA RMS
    - Visual acuity

- BCDVA (logMAR)
- UDVA (logMAR)

- Change from baseline in **OSI** vs. the change from baseline of following FVA parameters, respectively:
  - VMR
  - Starting visual acuity (LogMAR scale)
  - Minimal visual acuity (LogMAR scale)
  - Maximal visual acuity (LogMAR scale)

- Change from baseline in **variance of OSI** vs. the change from baseline of following FVA parameters, respectively:
  - VMR
  - Starting visual acuity (LogMAR scale)
  - Minimal visual acuity (LogMAR scale)
  - Maximal visual acuity (LogMAR scale)

8.2.3.2 Correlation Analyses for Lagged Data

Spearman's coefficients of correlation and its 95% confidence interval will be calculated for the following pairs of variables:

1) CFS vs. VMR

- Change from baseline in CFS at Month 1 vs. change from baseline in VMR at Month 2
- Change from baseline in CFS at Month 1 vs. change from baseline in VMR at Month 3
- Change from baseline in CFS at Month 2 vs. change from baseline in VMR at Month 3

2) CFS vs. LogMAR FVA

- Change from baseline in CFS at Month 1 vs. change from baseline in LogMAR FVA at Month 2
- Change from baseline in CFS at Month 1 vs. change from baseline in LogMAR FVA at Month 3
- Change from baseline in CFS at Month 2 vs. change from baseline in LogMAR FVA at Month 3

3) CFS vs. OSI

- Change from baseline in CFS at Month 1 vs. change from baseline in OSI at Month 2
- Change from baseline in CFS at Month 1 vs. change from baseline in OSI at Month 3
- Change from baseline in CFS at Month 2 vs. change from baseline in OSI at Month 3

4) CFS vs. Variance of OSI

- Change from baseline in CFS at Month 1 vs. change from baseline in variance of OSI at Month 2
- Change from baseline in CFS at Month 1 vs. change from baseline in variance of OSI at Month 3
- Change from baseline in CFS at Month 2 vs. change from baseline in variance of OSI at Month 3

5) CFS vs. VAS Symptom Score of Photophobia

- Change from baseline in CFS at Month 1 vs. change from baseline in VAS symptom score of photophobia at Month 2
- Change from baseline in CFS at Month 1 vs. change from baseline in VAS symptom score of photophobia at Month 3
- Change from baseline in CFS at Month 2 vs. change from baseline in VAS symptom score of photophobia at Month 3

6) CFS vs. VAS Symptom Score of Blurred Vision

- Change from baseline in CFS at Month 1 vs. change from baseline in VAS symptom score of blurred vision at Month 2
- Change from baseline in CFS at Month 1 vs. change from baseline in VAS symptom score of blurred vision at Month 3
- Change from baseline in CFS at Month 2 vs. change from baseline in VAS symptom score of blurred vision at Month 3

8.2.4 Graphical Analyses

Bar chart (with means and error bars at each visit) of the following variables will be generated, separately, to explore their pattern of evolution over time (from baseline to Month 3) under the IKERVIS® treatment:

- CFS score
- FVA parameters (VMR and LogMAR FVA)
- OSI
- Variance of OSI

9 SAFETY ANALYSES

The safety-related measures collected in this study include systemic and ocular AEs, corrected and uncorrected distance visual acuity, slit-lamp biomicroscopy, dilated fundus examinations, and IOP. The Safety population will be used for all safety summaries.

All the safety-related measures will be summarized descriptively. Except systemic AEs, which will be summarized at the subject level, all the other safety-related measures, including ocular AEs, will be summarized for the analysis eyes and fellow eyes separately.

9.1 Pre-treatment Events (PTEs) and Adverse Events (AEs)

PTEs and AEs are defined in Section 4.4.1. PTEs and treatment-emergent AEs (TEAEs) will be summarized separately.

In the overall AE summaries, subjects with any AE(s) will be tabulated by the following types of AEs:

- AEs
- SAEs
- Related AEs
  - AEs related to the study medication
  - AEs related to artificial tears
  - AEs related to study procedures
- AEs leading to premature discontinuation
- Sight threatening AEs
- Case of special interest
- Death

The above summaries will be repeated for ocular AEs in the analysis eye, ocular AEs in the fellow eye, and non-ocular AEs, respectively.

Besides the overall AE summaries listed above, AEs will be tabulated by SOC and PT. A subject who experienced multiple AEs within a SOC or PT will be counted only once for that SOC or PT, respectively. SAEs, related AEs, and serious related AEs will be tabulated similarly. Ocular and systematic AEs will also be summarized separately.

In addition, AEs will be tabulated by the following categories:

- SOC, PT, and maximal severity
- SOC, PT, and relationship (related to study medication, study procedure, or artificial tears)
- SOC, PT, maximal severity, and relationship (related to study medication, study procedure, or artificial tears)

Ocular AEs will be summarized for the analysis eye and fellow eye separately. Any ocular AE that occurred simultaneously to both eyes will be counted once for both the analysis eye and the fellow eye. Sight-threatening AEs and cases of special interest will be summarized by type of events specified in Section 4.4.1.2 and Section 4.4.1.3.

AEs, AEs leading to discontinuation, SAEs, sight-threatening AEs, case of special interest, and death, if any, will be listed separately.

9.2 Slit-lamp Biomicroscopy

For each biomicroscopy parameter rated on a 0-3 scale (0=None, 1=Mild, 2=Moderate, or 3=Severe) or 0-4 scale (0=None, 1=Mild, 2=Moderate, 3=Severe, and 4=Very severe), rating scores and shift from baseline will be summarized by analysis visit for the analysis eye and the fellow eye, separately. In addition, any worsening (increase) of ≥ 2 units from baseline will be listed.

For lashes, which are collected as Normal or Abnormal, rating scores and shift from baseline in status will be summarized by analysis visit for the analysis eye and the fellow eye, separately. Any worsening in status from Normal at baseline to Abnormal after baseline will be listed.

9.3 Uncorrected Distance Visual Acuity (UDVA)

UDVA will be collected on LogMAR scale and their values and change from baseline will be summarized, separately, using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum by analysis visit for the analysis eye and the fellow eye, separately.

9.4 Best Corrected Distance Visual Acuity (BCDVA)

BCDVA will be collected on LogMAR scale and their values and change from baseline will be summarized, separately, using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum by analysis visit for the analysis eye and the fellow eye, separately. Subjects with any BCDVA score of 2.0 or greater after baseline or BCDVA change from baseline ≥ 0.30 LogMAR will be listed.

9.5 Dilated Fundus Examination

Dilated fundus exam data will be collected as Normal or Abnormal. Rating scores and shift from baseline in status will be summarized by analysis visit for the analysis eye and the fellow eye, separately. Any worsening in status from Normal at baseline to Abnormal after baseline will be listed.

9.6 Intraocular Pressure

IOP and change from baseline in IOP will be summarized by analysis visit for the analysis eye and the fellow eye, separately. Subjects with any increase of ≥ 10 mmHg in IOP at any follow-up visit will be listed.

10 CHANGES FROM THE PROTOCOL

10.1 FVA Parameters to be Analyzed

The variable "FVA" was removed from the list of FVA parameters to be analyzed in Section 2.2.2.1 and Section 8.2.1 due to this variable was not in the FVA system outputs and not collected on the eCRF.

10.2 Scale Conversion of the FVA Parameters

FVA parameters (LogMAR FVA, starting VA, minimum VA, and maximum VA) were supposed to be collected on LogMAR scale on the eCRFs. However, due to the first time use of the FVA system by Santen and sites, and given the FVA system User Manual as well as the system outputs were all written in Japanese, there was some confusions regarding which numbers to be read off from the FVA system output. Instead of the LogMAR scores, the decimal VA scores were instructed to be recorded on the eCRFs. Therefore, at the data analysis stage, the following formula will be used to convert decimal VAs to LogMAR VAs before any data analyses are performed:

$$\text{LogMAR VA} = -\log_{10}(\text{decimal VA})$$

10.3 Sensitivity Analysis of the Primary Efficacy Endpoints

The protocol stated "Changes from baseline in VMR and variance of OSI will also be summarized by categorical change in CFS (-5, -4.5, -4, -3.5, -3, -2.5, -2, -1.5, -1, 0, +1 unit change) and by analysis visit (Month 1, Month 2, and Month 3)." (Section 12.3 of the protocol). This is now changed to "Changes from baseline in VMR and variance of OSI will also be summarized by categorical change in CFS (-5, -4.5, -4, -3.5, -3, -2.5, -2, -1, 0, +1 and +2-unit change) and by analysis visit (Month 1, Month 2, and Month 3)." in Section 8.1.2 of this SAP to fix some typographical errors in the categories.

10.4 Correlation Analysis for Data Collected from the Same Visit

Correlation analyses were added to Section 8.2.3.1 for correlation between the change from baseline in CFS vs. change from baseline in TBUT, Schirmer's test, HOA RMS, VAS symptom scores (photophobia and blurred vision, separately), and visual acuity (BCDVA and UDVA, separately). Also added were correlation between the change from baseline in logMAR FVA vs. change from baseline in OSI parameter (OSI and variance of OSI, separately), TBUT, Schirmer's test, HOA RMS, VAS symptom scores (photophobia and blurred vision, separately), and visual acuity (BCDVA and UDVA, separately).

10.5 Correlation Analysis of the Lagged Data – Change from Baseline in CFS vs. Change from Baseline in VAS Symptom Scores

Two lagged analyses were added to Section 8.2.3.2 to check the correlation between the change from baseline in CFS vs. the lagged change in VAS symptom scores (photophobia and blurred vision, separately).

11 REFERENCES

1. Laird, Nan M.; Ware, James H. (1982). Random-Effects Models for Longitudinal Data. *Biometrics*, **38** (4): 963–974.

2. Lindstrom, ML; Bates, DM (1988). Newton-Raphson and EM algorithms for linear mixed-effects models for repeated-measures data. *JASA*, **83** (404): 1014–1021.

12 APPENDICES

12.1 Appendix A. Slit Lamp Grading

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

0 = None (none are plugged).

1 = Mild (1 to 2 glands are plugged).

2 = Moderate (3 to 4 glands are plugged).

3 = Severe (All glands are plugged).

Lid - Erythema

0 = None (normal).

1 = Mild (redness localized to a small region of the lid(s) margin OR skin).

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

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

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

Lid - Oedema

0 = None (normal).

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

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

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

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

Lashes

0 = Normal

1 = Abnormal (specify)

Conjunctiva – Erythema

0 = None (normal).

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

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

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

Conjunctiva - Oedema

0 = None (normal).

1 = Mild (slight localized swelling).

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

3 = Severe (severe diffuse swelling).

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

Tear Film Debris

0 = None (absence of debris).

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

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

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

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

Anterior Chamber Inflammation (Slit beam= 0.3 mm wide, 1.0 mm long)

0 = None (no Tyndall effect).

1 = Mild (Tyndall effect barely discernible).

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

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

Lens

0 = No opacification (normal lens).

1 = Mild lens opacification.

2 = Moderate lens opacification.

3 = Severe lens opacification.

Vitreous

0 = No haze (normal lens).

1 = Mild vitreous haze.

2 = Moderate vitreous haze.

3 = Severe vitreous haze.

12.2 Appendix B. Sample SAS Codes for Inferential Analyses

(1) Spearman Correlation Analysis.

For the primary efficacy endpoint:

```
ods output SpearmanCorr = outdata;
proc corr data = indata spearman;
  where visitnum = 3 and analysis_eye = "Y";
  var CFSchg;
  with VMRchg;
run;
```

- In the *outdata* dataset obtained from the above procedure,
  - n = nCFSchg
  - correlation coefficient = CFSchg
  - p-value = pCFSchg.

For the secondary efficacy endpoint:

```
ods output SpearmanCorr = outdata;
proc corr data = indata spearman;
  where visitnum > 0 and analysis_eye = "Y";
  var CFSchg;
  with VMRchg;
  by visitnum;
run;
```

- In the *outdata* dataset obtained from the above procedure,
  - n = nCFSchg
  - correlation coefficient = CFSchg
  - p-value = pCFSchg.

(2) Sensitivity Analysis for the primary efficacy endpoint – the MMRM model.

Please only use the observed (i.e., non-imputed) data for this analysis.

```
ods output SolutionF = outdata1;
proc mixed data = indata method = ml;
  where visitnum > 0 and analysis_eye = "Y";
  class visitnum subjid;
  model VMRchg = CFSchg visitnum Base_CFS / noint solution ddfm=KR;
  random int / subject = subjid type = UN;
run;

ods output Tests3 = outdata2;
proc mixed data = indata method = ml;
  where visitnum > 0 and analysis_eye = "Y";
  class visitnum subjid;
  model VMRchg = CFSchg visitnum Base_CFS / solution ddfm=KR;
  random int / subject = subjid type = UN;
run;
```

- Slope estimate ("Estimate") and standard error ("StdErr") will be obtained from the *outdata1* dataset where EFFECT = "CFSchg".
- P-value ("ProbF") will be obtained from the *outdata2* dataset where EFFECT = "CFSchg".
- Steps for choosing the covariance structure in the RANDOM statements above:
  1) Start with TYPE = UN. If the model converges, then stop here and get the results from this model.
  2) If the model does not converge, then try to replace UN with TOEPH, ARH(1), TOEP, AR(1), CS, and VC sequentially, and stop when the model converges, or keep going if model does not converge until the convergence criteria are met.
  3) Please record which covariance structure is used for which model and put that in the table footnote.
  4) Please note that the model covariance structure can be different for different independent variable/dependent variable combinations. But it should be the same for the two procedures used above for the same independent variable/dependent variable combination. Choose the covariance structure that converges for both procedures.