Statistical Analysis Plan 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
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STATISTICAL ANALYSIS PLAN

Protocol NVG14L127

Protocol Title:	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 subjects with severe keratitis receiving IKERVIS® (1mg/ml ciclosporin) eye drops
Product:	IKERVIS® (1mg/mL Ciclosporin)
Protocol Number:	NVG14L127
Sponsor:	Santen SAS Genavenir IV, 1 rue Pierre Fontaine F-91058 Evry, France
Date:	September 1st, 2023
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[redacted]

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ABBREVIATIONS

Abbreviation	Explanation
ADaM	Analysis Data Model
ADR	adverse drug reaction
AE	adverse event
AT	Artificial Tears
ATC	Anatomical-Therapeutic-Chemical
BCDVA	best-corrected distance visual acuity
CI	confidence interval
CFS	Corneal Fluorescein Staining
CM	concomitant medications
CSI	case of special interest
CSR	clinical study report
eCRF	electronic case report form
DED	dry eye disease
DEQS	Dry Eye-related Quality-of-Life Score
FAS	full analysis set
QD	quaque die
QoL	quality of life
IOP	intraocular pressure
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LogMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MH	medical history
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
OU	oculus uterque (both eyes)
PPS	per-protocol set
PT	preferred term
SAE	serious adverse event
SANDE	Symptom Assessment iN Dry Eye questionnaire
SAP	statistical analysis plan

Abbreviation	Explanation
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SOC	system organ classification
TBUT	Tear Breakup Time
TEAE	treatment-emergent adverse event
VA	Visual Acuity

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods and analyses to be implemented for the data collected from the IKERVIS PAES study within the scope of Santen's 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 subjects with severe keratitis receiving IKERVIS® (1mg/ml ciclosporin) eye drops". It applies to the study protocol Amendment 1 (version 3.0), dated 17-OCT-2018, 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. Deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the CSR.

REVISION HISTORY FROM THE PREVIOUS VERSION (1.0):

- Reflected the latest version of MedDRA (Sec. 4.4)
- Updated the definitions of ocular surface complication (Sec. 4.4.1.1)
- Updated analysis set (Sec. 6)
- Added Sjogren patient population summary (Sec. 7 and 8)
- Added medical history summary for period 2 (Sec. 7.5)
- Added CFS shift table (Sec. 8.2)
- Added CFS complete resolution summary (CFS=0 at post BL) (Sec. 8.2)
- Added MMRM to estimate treatment difference for secondary endpoints (Sec. 8.2) and updated related section (Sec. 5.1 and 5.4)
- Clarified the duration of detail for ocular surface complication (Sec. 9.1)
- Added SAS sample code (Sec. 12)

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objectives of this 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) subjects 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.

The secondary objectives of this study 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 subjects, 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.

2.2. Endpoints

2.2.1. Primary Efficacy and Safety Endpoints

- The correlation between 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 of ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity and ocular infection
- Time to onset of ocular surface complications

2.2.2. 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 during Period 1)

- 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 subpopulation,

- Dry Eye related Quality of life Score (DEQS) summary scores, and change from baseline at Month 6, Month 9, and Month 12 will be presented for Period 1. 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:

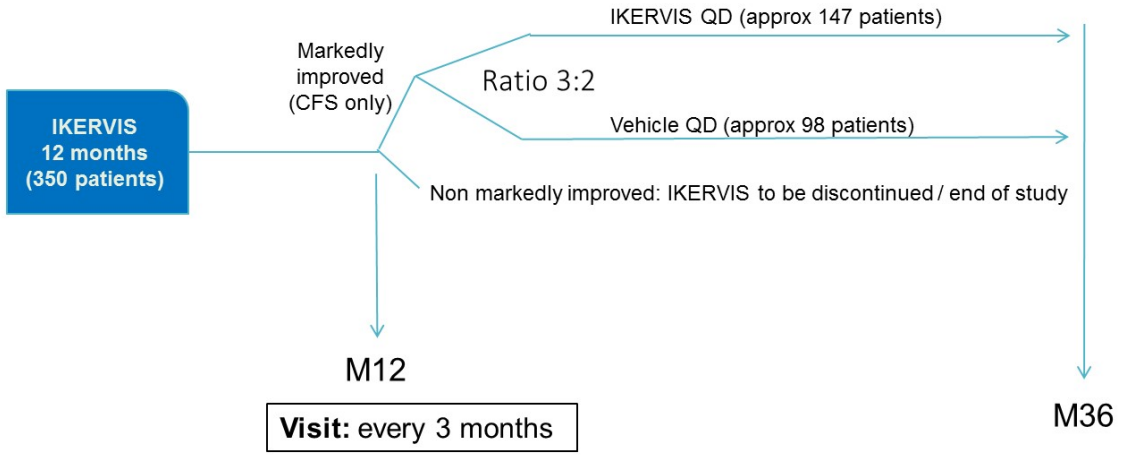
- Intraocular pressure (IOP) and change from baseline at Month 12, Month 24 and Month 36 visits
- Best Corrected Distance Visual Acuity (BCDVA) and change from baseline at Month 6, Month 12, Month 24 and Month 36 visits
- Incidence and severity of ocular and systemic adverse events (AEs) over the three-year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

3. STUDY DESIGN

3.1. General Study Design

This is 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 subjects with severe keratitis receiving IKERVIS® (1mg/ml ciclosporin) eye drops. All enrolled subjects will enter a period of 12 months of treatment (Period 1) with open-label IKERVIS® treatment [once daily (QD) into the affected eye(s) at bedtime]. At Month 12 visit, markedly improved subjects will continue the study for an additional 24 months randomized, double-masked treatment period (Period 2) to receive either IKERVIS® QD or vehicle QD (at a ratio of 3:2), Figure 1.

Figure 1. Study Design Diagram



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

Markedly improved subjects are defined as subjects having a corneal fluorescein staining (CFS) score improvement from baseline of 2 grades or more on the modified Oxford scale [unless if the subject had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more] in the study eye. Subjects who are not markedly improved at Month 12 based on the above definition will be terminated from the study.

This study will be conducted in about 36 sites located in European and non-European countries.

3.2. Randomization 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 subject 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 region (Europe vs. non-Europe), and the permuted block randomization will be used within each stratum.

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 subject's management), the investigator is entitled to unmask the subject 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 unmasking. The details of this unmasking procedure will be described in a separate document. Subjects unmasked for the management of a SAE will be discontinued from the study.

3.3. Sample Size Determination

The 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 randomized 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 us 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 subjects, a lower-bound of the estimated complication rate was 4% in severe DED subjects. 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.

3.4. Visits and Assessments

There are 5 scheduled visits for each subject in Period 1 (open-label treatment period, Day 1 Visit to Month 12 Visit) and 8 additional visits for markedly improved subjects who enter Period 2 (double-masked treatment period, Month 12 Visit to Month 36 Visit). Assessments at each visit and the visit window for each post-baseline assessment are specified in the Assessment Schedule shown on Table 1.

Table 1. 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						
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	
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]

	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
Registration of subjects 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
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 subject 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 subjects at Month 12 visit.*

[I] *Dispensation of masked study medication (IKERVIS® or Vehicle).*

4. DEFINITIONS

4.1. Time-Related Terms

4.1.1. Baseline Visit

For this study, the *baseline visit* is the Day 1 Visit when a subject was enrolled into this study (as a non-screen failure subject who signed informed consent) and received open-label IKERVIS treatment in Period 1.

4.1.2. Treatment Start Date and End Date

The *treatment start and end dates* for each treatment period and the study are defined as follows:

Treatment Period	***Treatment Start Date***	***Treatment End Date***
Open-Label Treatment Period (Period 1)	The date of the first dose of the open-label IKERVIS treatment (or Day 1 date)	The date of the last dose of the open-label IKERVIS treatment • The date of the day before the Month 12 Visit will be considered the Period 1 treatment end date for subjects who completed Period 1 treatment. • The date of the day before the Exit Visit will be used for subjects who prematurely discontinued from the study. If the Exit Visit date of a non-completer is not available, then the day before the last available visit date will be considered the treatment end date.
Double-Masked Treatment Period (Period 2)	The date of the first dose of the double-masked study treatment (or Month 12 Visit date)	The date of the last dose of the double-masked study treatment • The date of the day before the Month 36 Visit will be considered the Period 2 treatment end date for subjects who completed the study. • The date of the day before the Exit Visit will be used for subjects who prematurely discontinued from the study. If the Exit Visit date of a non-completer is not available, then the day before the last available visit date will be considered the treatment end date.

For each treatment period, the treatment end date will be set to missing if the treatment start date is missing.

4.1.3. Study Day

The *study day* describes the relative day of an observation starting with the reference date designated as Study Day 1. In this study, the treatment start date is the reference date.

For Period 1 and entire study period, the study day will be calculated as:

Study Day = Date – Period 1 Treatment Start Date + 1

For subjects who entered Period 2 (i.e., got randomized), their *Period 2 study day* will be calculated as:

Period 2 Study Day = Date – Period 2 Treatment Start Date + 1

4.1.4. Analysis Visit and Analysis Window

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 a measurement should be mapped to.

The following *analysis windows* will be applied to minimize the amount of missing data for analysis purposes:

Analysis Visit (Target Study Day)	***Protocol Visit Window***	***Analysis Window***
Period 1	(Refers to Study Day for the entire study period)	(Refers to Period 1 Study Day)
Baseline (Day 1)	[1, 1]	[-, 1]
Month 3 (Day 90)	[83, 97]	[2, 135]
Month 6 (Day 180)	[173, 187]	[136, 225]
Month 9 (Day 270)	[263, 277]	[226, 315]
Month 12 (Day 360)	[353, 367]	[316, ET in Period 1 or Randomization First Dose Date in Period 2]
Period 2	(Refers to Study Day for the entire study period)	(Refers to Period 2 Study Day)
Month 12 (Day 360)	[353, 367]	[-, 1(First Dose Date in Period 2)]
Month 15 (Day 450)	[443, 457]	[2, 135]
Month 18 (Day 540)	[533, 547]	[136, 225]
Month 21 (Day 630)	[623, 637]	[226, 315]
Month 24 (Day 720)	[713, 727]	[316, 405]
Month 27 (Day 810)	[803, 817]	[406, 495]
Month 30 (Day 900)	[893, 907]	[496, 585]
Month 33 (Day 990)	[983, 997]	[586, 675]
Month 36 (Day 1080)	[1073, 1087]	[676, 765]

ET= Early Termination.

The analysis visit of a measurement will be determined based on the study day of the measurement and specified analysis window, and is not necessarily the same with the protocol study visit where the measurement was collected. 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 latter one will be selected for that visit.

4.1.5. Extent of Exposure

The *extent of exposure* (*days*) to study medication will be assessed by duration of treatment exposure.

- For subjects who only received study treatment in Period 1 and exited the study, their duration of treatment exposure will be derived as:

  Duration of IKERVIS exposure =

  (Period 1 Treatment end date – Period 1 Treatment start date) + 1

- For subjects who entered Period 2 and received IKERVIS treatment, their duration of treatment exposure will be derived as:

  Duration of IKERVIS exposure =

  (Period 2 Treatment end date – Period 1 Treatment start date) + 1

- For subjects who entered Period 2 and actually received the Vehicle treatment, their duration of treatment exposure will be derived as:

  Duration of IKERVIS exposure =

  (Period 1 Treatment end date – Period 1 Treatment start date) + 1

  Duration of Vehicle exposure =

  (Period 2 Treatment end date – Period 2 Treatment start date) + 1

4.2. Endpoint-Related Definitions

4.2.1. Study Eye and Fellow Eye

The study eye will be the 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 not discriminant, the eye with the lowest Schirmer test value will be chosen. If not discriminant, the right eye will be chosen as the study eye. The other eye will be the non-study eye, or fellow eye.

4.2.2. Baseline Score

The *baseline score* is the observed measurement at Baseline (Day 1).

In addition, for subjects who got randomized in Period 2, the observed measurements made at Month 12 Visit will be used as baseline scores for Period 2. If a Month 12 measurement is

missing, the last observed measurement or derived score prior to the first dose of the Period 2 double-masked study treatment will be used to impute the baseline score for Period 2.

4.2.3. Change from a Reference Point

For Period 1 and Entire Study analyses, the change from baseline at a post-baseline visit will be derived as:

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

For Period 2 analyses, change from Month 12 will be the change used in the analyses.

4.3. Efficacy-Related Definitions

4.3.1. SANDE Global Score

The SANDE global score will be calculated using the following formula:

$$\text{SANDE Global Score} = \sqrt{(\text{Frequency of symptom score}) \text{ x } (\text{Severity of symptom score})}$$

If frequency or severity will be missing for a subject at the same visit, the SANDE global score will be missing.

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

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

The DEQS includes two subscales, which first assess the *frequency* of the symptoms and disability (0 to 4) and then assess symptom *degree* (1 to 4).

The DEQS **overall *frequency* of impairment score** will be calculated with the following formula (Inomata et al., 2020; Sakane et al., 2013):

$$\text{score} = \frac{(\text{sum of the Frequency scores of all questions answered}) \times 25}{\text{total number of questions answered}}$$

The DEQS **overall *degree* of impairment score** will be calculated by the following steps:

1. For all questions with the *frequency* score (Column A) 0, set the *degree* score (Column B) to 0.
2. Calculate overall *degree* score with the formula:

$$\text{score} = \frac{(\text{sum of the Degree scores for all questions answered}) \times 25}{\text{total number of questions answered}}.$$

The summary scores range from 0 to100, with a higher score representing greater disability.

4.3.3. Conjunctival Fluorescein Staining Total Score

Conjunctival fluorescein staining total score will be the sum of conjunctival fluorescein staining score from nasal and temporal sides.

4.3.4. Markedly Improved Status

Markedly improved patients are defined for the Period 1 portion of study. The markedly improved status is defined as:

- If a subject's study eye had CFS score of 3 or 4 at Baseline, the improvement in CFS score at a post-baseline visit has to be 2 or more on the modified Oxford scale.
- If a subject's study eye had a CFS score of 5 at Baseline, the improvement in CFS score at a post-baseline visit has to be 3 grades or more on the modified Oxford scale.

4.3.5. Relapse Status

For this study, the relapse status is defined as an increase of CFS score of 2 or more on the modified Oxford scale (compared to CFS score at Month 12) during Period 2.

4.4. Safety-Related Definitions

4.4.1. Adverse Event

Under the Protocol NVG14L127, 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.

An *on-study* AE can occur any time after the date of informed consent through the last study visit. An AE will be considered as *treatment-emergent* if the onset date of the AE occurred on or after the treatment start date of the analysis period. Treatment-emergent AEs (TEAEs) are a subset of on-study AEs. Both on-study and TEAEs will be collected, but only TEAEs will be tabulated.

The severity of each AE will be graded by the Clinical Investigator as Mild, Moderate, or Severe. AEs will be rated by the Investigator as to their causality/relationship to the study drug.

Each AE will be classified into a system organ class (SOC) and coded to a preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), version 23.1 published in 2020.

4.4.1.1. Ocular Surface Complications

Under the Protocol NVG14L127, *ocular surface complication* is defined as the occurrence of any AE defined as corneal ulceration, corneal perforation, loss of visual acuity, or ocular infection.

4.4.1.1.1. Ocular Infection

Ocular infection is defined as any ocular events (location reported as "ocular") under SOC "Infections and infestations."

4.4.1.1.2. Corneal Perforation

Corneal perforation is defined as PT of "Corneal perforation."

4.4.1.1.3. Corneal Ulceration

Corneal ulceration is defined as PT of "Ulcerative keratitis."

4.4.1.1.4. Loss of Visual Acuity

Loss of visual acuity is defined as all PTs under HLT "Visual impairment and blindness" except for PT of "colour blindness".

The list of AEs will be reviewed based on the above four definitions via a data review meeting.

4.4.1.2. Serious Adverse Event

An AE will be counted as a *serious adverse event* (SAE) if the Clinical Investigator selected "Yes" to the question 'Is the adverse event serious?' on the AE eCRF. A serious AE 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-subject 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 subject 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 subject 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 subject 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

4.4.1.3. Case of Special Interest (CSI)

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

- CSI related to 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)
- CSI related to medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or subject
  - 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.
  - Abuse of study drug: Persistent or sporadic, intentional excessive use of medicinal product which is accompanied by harmful physical or psychological effects.
  - Other

4.4.1.4. Ocular Adverse Event

An AE will be counted as an *ocular AE* if the Clinical Investigator selected “OD”, “OS”, or “OU” under ‘Eye(s) affected’ on the AE eCRF.

4.4.1.5. Adverse Drug Reactions (ADR)

An AE will be counted as an *adverse drug reaction* (ADR) if the Clinical Investigator answered ‘Related’ to the AE eCRF question “Relationship to Study Drug”.

4.4.2. Other Safety Measures

Table 2 lists the safety measures to be evaluated for this study.

Table 2. Safety Assessments

Safety Measures	Note
Intraocular pressure (IOP)	IOP will be measured on both eyes at Baseline, Month 12, Month 24, and Month 36.
Best-corrected distance visual acuity (BCDVA)	BCDVA will be measured for each eye at Baseline, Month 6 and Month 12 in Period 1 and at Month 18, Month 24, Month 30, and Month 36 in Period 2 using a Snellen chart. BCDVA in Snellen scale will be converted to logMAR scale using the following equation and be used in all the BCDVA analyses: $\text{LogMAR VA} = -\log_{10}\left(\frac{\text{Snellen numerator}}{\text{Snellen denominator}}\right)$
Slit-lamp Biomicroscopy	Slit-lamp biomicroscopy examinations will be performed at Baseline, Month 6 and Month 12 in Period 1 and at Month 18, Month 24, Month 30, and Month 36 in Period 2. Grading of the Meibomian glands, lids, lashes, conjunctiva, tear film debris, anterior chamber and lens will be done on an ordinal scale. Cataract severity will be assessed for phakic eyes only.

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 study medication start date. *Concomitant medication* is defined as any non-study medication taken concurrently while receiving study medication, i.e., the treatment period (period of time from first dose to last dose) of a concomitant medication taken by a subject must overlap with the treatment period (period of time from first dose to last dose) of the study medication.

All prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Global, Version September 2019, format B3. Each prior or concomitant medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO Drug preferred drug name.

4.5.2. Concurrent Medical Conditions

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

5. GENERAL CONSIDERATIONS

All measures will be summarized for Overall subjects in Period 1 and by treatment group in Period 2 as well as for the entire study descriptively. 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 (%).

Unless otherwise specified, the following conventions on decimal places will be followed in reporting numerical results.

Statistic	**Reporting Decimal Places**
Range (Low Value, High Value)	Recorded decimal places
Mean, Median	Recorded value + 1 decimal places
Confidence interval, standard deviation, standard error	Recorded value + 2 decimal places
P-value	4 Decimal places (ex. 0.0021)

No statistical testing will be conducted for both the efficacy and safety measures for Period 1 in this study.

All data summary/analysis will be performed using SAS Version 9.4 or later. Individual data, including relevant derived variables, will be listed. Additional analyses not specified in this SAP may be conducted if deemed necessary and will be documented in the CSR.

5.1. Adjustments for Covariates

For better understanding the long-term efficacy of IKERVIS, model based analysis (MMRM) will be conducted with corresponding baseline of each endpoint and geographic region (Europe vs. non-Europe) as covariates. The detail of each model will be described in Section 8.

5.2. Handling of Missing Data

No imputation for missing data will be performed on any efficacy and safety endpoints. Unless specified otherwise, descriptive summaries will be based on observed cases.

Completely or partially missing onset and resolution dates for AEs, Concomitant Medications (CM), and Medical History (MH) will be imputed in a conservative fashion as follows:

Incomplete Adverse Event Onset Date

1. *Year imputation*
    - If *year* is missing (or AE onset date is completely missing), then the onset date will not be imputed.
2. *Month imputation*
    - If *year* is not missing but *month* is missing, then:

- If *year* = year of first study dose date, then set the *month* and *day* to the day and month of first study dose
- Else if *year* ≠ year of first study dose: set *month* to January

3. *Day imputation*
   - If *day* is missing (*month and year* not missing), then:
     - If *year* = year and *month* = *month* of first study dose, then set *day* to day of first study dose
     - Else if *year* ≠ *year* and *month* ≠ *month* of first study dose, then set *day* to first day of the *month* in the year

Incomplete Adverse Event Resolution Date

Do not impute if any resolution date is missing.

If the duration of AE is needed, the following approach may be considered:

- If *year* is missing (or AE resolution date is completely missing): do not impute
- If *year* is not missing but *month* and *day* are missing: impute December 31st for missing *month* and *day*
- If *year* and *day* are not missing but *month* is missing: impute December for missing *month*
- If *year* and *month* are not missing but *day* is missing: impute last day of the *month* for missing *day.*

Incomplete CM or MH Onset Date

1. If *year* is missing (or CM/MH onset date is completely missing), do not impute
2. If *year* is not missing but *month* and *day* are missing, impute January 1st for missing *month* and *day*
3. If *year* and *day* are not missing but *month* is missing, impute January for missing *month*
4. If year and month are not missing but day is missing, impute 01 for missing day

Incomplete CM or MH Resolution Date

1. If a resolution date is completely missing, do not impute.
2. If year is not missing but month and day are missing, use the last day of the year to impute the missing month and date parts of the resolution date.
3. If year and month are not missing but day is missing, use the last day of the month to impute the missing date part of the resolution date

5.3. Multi-Center Studies

This study will be conducted in about 36 sites located in European and non-European countries. Sites will not be pooled for any inferential analysis.

5.4. Multiple Comparisons / Multiplicity

The objective of this study is to better understanding of long-term efficacy for exploratory purpose. No multiple comparison will be planned.

5.5. Interim Analysis

There is one interim analysis planned for this study. The purpose of the interim analysis is to present appropriate summary of data collected for the period 1. Interim analysis will be conducted once all subjects will have completed their Month 12 Visit or withdrawal visit.

Data cut criteria for this interim analysis is shown in Table 3.

Table 3 Data Cut Plan for Interim Analysis

Analysis Data	Data Example	Data Cut Criteria
Visit Data	IOP, TBUT, DEQS, etc. that are collected on visit date	Data collected at Month 12 or earlier will be included.
Non-visit Data	AE, medication, procedures, CSI, etc.	Incidents that happened up to the day of the first dose in Period 2 study drug will be included in the analysis.

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.

6. ANALYSIS POPULATION

Analysis populations defined for each analysis period are as follows.

For Period 1:

- The **FAS (Full Analysis Set) Period 1** 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 of Period 1.
- The **PPS (Per-Protocol Set) Period 1** 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 Period 1** consists of all subjects 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 **Sjögren Patients Population** consists of subjects who were known to have diagnostic status of the Sjögren disease based on the medical history obtained at baseline.
- The **Subjects Markedly Improved during Period 1** are defined as FAS subjects who achieve CFS score improvement from baseline of 2 grades or more (unless if the subject had a CFS score of 5 at baseline, the improvement in CFS has to be 3 grades or more) at anytime during Period 1.

For Period 2 and Entire Study:

- The **FAS Period 2 (or FAS Entire Study)** population consists of all randomized subjects who received at least one dose of the double-masked 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 Period 2 (or PPS Entire Study)** will be a subset of FAS Period 2, 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 Period 2 (or Safety Population Entire Study)** consists of all subjects randomized in Period 2 who received at least one dose of the double-masked study medication and for whom any follow-up information is available in Period 2. It will be the analysis population for safety analyses to be performed with subjects as treated.
- The **Sjögren Patients Population** (**Period 2 or Entire Study)** consists of subjects who were known to have diagnostic status of the Sjögren disease based on the medical history obtained at baseline and satisfies FAS Period 2 or Safety Population Period2 criteria depending on analysis.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

The disposition of all subjects who are enrolled in Period 1 will be presented in a table. The disposition summary will include the number and percentage of subjects in FAS Period 1, PPS Period 1, Safety Population Period 1, completers and non-completers at Month 12 Visit. In addition, Sjögren Patients in Period 1, Subjects Markedly Improved in Period 1 will also be presented.

In addition, the subject enrollment will be summarized by geographic region, country, and site.

Subject disposition of Period 2 will be presented in a separate table in terms of all subjects who are randomized in Period 2 by treatment and overall. The summary will include the number of subjects in the FAS Period 2, PPS Period 2, Sjögren Patients in Period 2, and Safety Population Period 2 as well as completers and non-completers at Month 36 Visit along with the primary discontinuation reason.

The subject distribution of randomized subjects in Period 2 will also be summarized by geographic region, country, and site.

7.2. Demographics and Other Baseline Characteristics

For Period 1 summary, subject demographics and baseline characteristics will be summarized for the FAS Period 1 population, the Sjögren Patients Population, and the Markedly Improved Subjects in Period 1. The descriptive summary will be repeated for the FAS Period 2 population for each treatment group and overall for Period 2 summary and Sjögren Patients to satisfy FAS Period 2. The Entire Study summary will not be provided because the FAS Entire Study population is same as the FAS Period 2 population.

For subject demographics, the following variables will be summarized:

- Age at enrollment (continuous and categorical: < 65 years or ≥ 65 years)
- Sex (categorical: male or female)
- Ethnicity (categorical: Hispanic/Latino or Not)
- Race (categorical: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other)

For baseline characteristics, the following variables will be summarized for study eye (summarize for fellow eye if needed):

- CFS Score on the Modified Oxford Scale (<3 and each category)
- Schirmer test without anaesthesia (<10 mm/5 min or ≥10 mm/5 min)
- Symptom Score (Number of subjects with a score ≥ 2)
- Primary diagnosis (dry eye disease: both eyes or single eye)
- Duration of dry eye disease (years)

- Sjögren Disease status (yes or no) where appropriate
- Alcohol use [yes or no; if yes, ≤ 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 or no)
- Tobacco use
    - Yes
        - Ex-smoker (number of packets per year and duration of smoking)
        - Current smoker (number of packets per year and duration of smoking)
    - No
        - Passive tobacco use (yes, no)

7.3. Medical History

For this study, medical and surgical history and adverse events will be coded using MedDRA 23.1. Each medical event will be classified into a SOC and mapped to a Preferred Term (PT).

The medical and surgical history will be summarized for the FAS Period 1 population, the Sjögren patients population, and the subjects markedly improved in Period 1. Subjects reporting any medical and surgical history at baseline will be tabulated by SOC and PT for each planned treatment and overall. These will be also summarized for the FAS Period 2 population and Sjögren Patients to satisfy FAS Period 2.

7.4. Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Informed consent
- Inclusion/exclusion criteria
- Concomitant treatment
- Investigational product
- Procedures/tests/assessments
- Protocol Implementation
- Randomization
- Safety reporting
- Time Window
- Other

A protocol deviation is considered important 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 important protocol deviations prior to database lock.

The protocol deviations will be summarized for Period 1 and Period 2 separately using the FAS Period 1 subjects and the FAS Period 2 respectively. Subjects with any important protocol deviations will be tabulated by deviation category by study period and for each planned treatment and overall for Period 2. In addition, important protocol deviations will also be listed.

7.5. Prior and Concomitant Medications

Non-study medications will be categorized into prior medications and concomitant medications. Specifically, the *prior medication* is defined as any non-study medication taken and ended prior to the treatment start date. The *concomitant medication* is defined as any non-study medication taken concurrently while on the study medication, i.e., the treatment period of a concomitant medication taken by a subject needs to overlap with his/her treatment period of the study medication.

For this study, non-study medications, including prior and concomitant medications, will be coded using WHO Drug, Version Enhanced (September 2019) format B3. Each non-study medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO Drug preferred drug name.

Non-study medications will be summarized for the Safety population. Prior medications will be summarized for both the Safety Population Period 1 and Period 2. Concomitant medications will be summarized by study period. For Period 2, concomitant medications will be summarized by each actual treatment received and overall. A subject will be counted at most once for each medication per period, even if the subject took the same medication on multiple occasions. In addition, prior medications and concomitant medications will also be listed, separately.

For the Sjögren patients population, prior and concomitant medication uses will be summarised separately.

7.6. Treatment Compliance

Compliance to the study medication use is tracked on the Compliance eCRF as the number of single dose medication containers not used and returned.

Due to the irregularities in returning containers caused by COVID-19 situation, the treatment compliance will be assessed by study period rather than by intervals based on scheduled visits as specified in the protocol. Since some visits, for example, happened remotely, dispensing or returning of study drug could not happen on a scheduled time. Compliance rate will be calculated for Period 1, and Period 2, respectively.

For a given analysis period, compliance rate will be calculated using the following formula, which assumes that the unreturned containers are not used:

Treatment Compliance Rate (%) in Period x

$$= \frac{\text{No. of dispensed containers}-(\text{No. of returned unused containers} + \text{No. of unreturned containers})}{\text{Duration of Period x}} \times 100$$

where the Duration of Period x is the number of days subjects should have administered study medication in the analysis period, calculated as

Duration of Period x = end date of study drug in Period x – start date of study drug in Period x.

Compliance rate of ≥ 80% will be treated as compliant. Compliance will be summarized continuously and categorically (compliant and non-compliant) for FAS subjects for Period 1 and Period 2 separately. Period 2 summaries will be performed by planned treatment and overall.

7.7. Exposure to Study Medication

The *extent of exposure* to study medication will be assessed by duration of treatment exposure, derived as:

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

Specially,

Period	**Treatment Start Date**	**Treatment End Date**
Period 1	Period 1 treatment start date	Period 1 treatment end date
Period 2	Period 2 treatment start date	Period 2 treatment end date
Entire Study Period (for subjects who entered Period 2 and received IKERVIS treatment only)	Period 1 treatment start date	Period 2 treatment end date

For subjects in the Safety Population, the duration of exposure will be summarized using descriptive statistics continuously and categorically for Period 1, Period 2 (by actual treatment received and overall), and for the entire study (for subjects who entered Period 2 and received treatment (IKERVIS/IKERVIS or IKERVIS/Vehicle) or for subjects who received IKERVIS treatment during Period 1 or 2) separately.

The duration of exposure categories are:

- Period 1: 1-90, 91-180, 181-270, or ≥ 271 days
- Period 2: 1-90, 91-180, 181-270, 271-360, 361-450, 451-540, 541-630, ≥ 631days
- Entire study period: 1-90, 91-180, 181-270, 271-360, 361-450, 451-540, 541-630, 631-720, 721-810, 811-900, 901-990, or ≥ 991 days

8. EFFICACY ANALYSES

Unless otherwise specified, all efficacy analyses will be performed on the study eyes of the FAS Period 1 population, the Sjögren Patients in Period 1, the Subjects Markedly Improved in Period 1, the FAS Period 2 population, the FAS Entire Study population, and Sjögren Patients to satisfy FAS Period 2 (or FAS Entire Study Population) .

8.1. Analysis of Primary Efficacy Endpoint

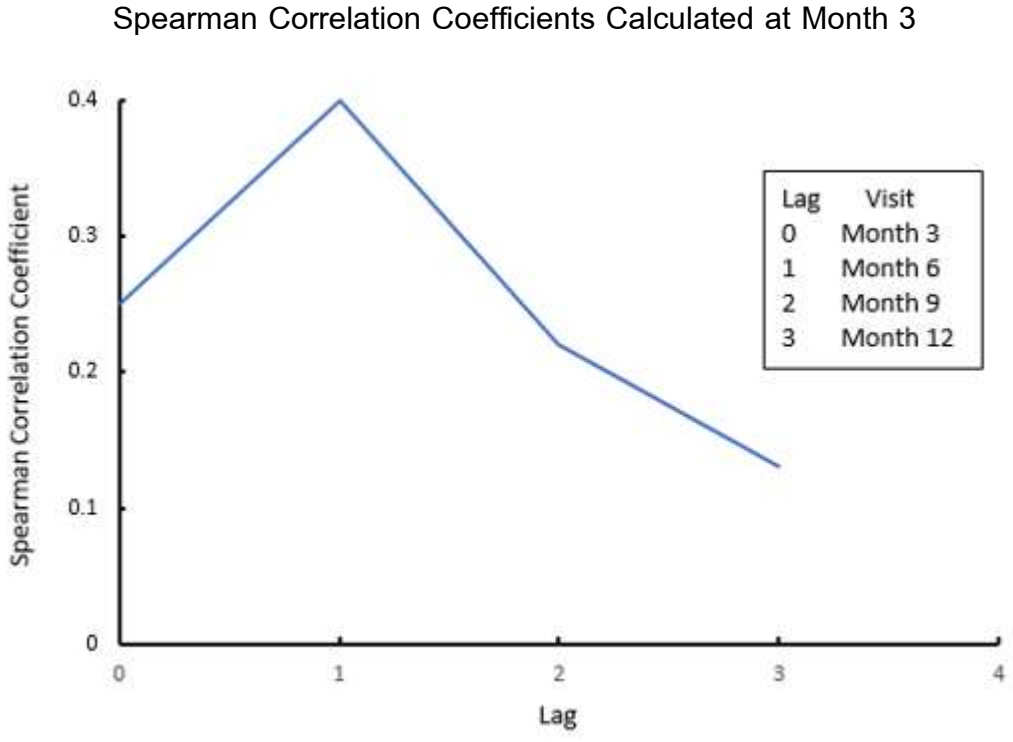
The primary efficacy endpoint is the correlation between change from baseline in CFS score and SANDE symptoms score at each visit, and cross correlation of sign at visit X versus symptoms at visit X+i, if any. Missing data will not be imputed.

8.1.1. Primary Analysis

For Period 1 analysis, Spearman correlation coefficient and its 95% confidence interval will be calculated for the correlation analysis between change from baseline in CFS score at visit X and SANDE symptoms score at each visit X+i in period 1 using the FAS Period 1 population.

The primary efficacy endpoint analysis result will be presented graphically by plotting Spearman correlation coefficients calculated at each visit. Spearman correlation coefficients will be plotted for the timepoints where more than 2 lagtime correlations are calculated. The plots will have x-axis to show lags, i, and y-axis to show Spearman correlation coefficients as shown in Figure 2, which is for X = Month 3.

Figure 2. A Sample Plot of Correlation between Change from Baseline in CFS Score at Visit X vs. Change from Baseline in SANDE Score at Visit X + i



Interpretation of the results from graphical analysis:

- If any individual graph shows a "bump" or a plateau at any lag > 0 point, as shown in Figure 2, it would be considered as an indication of existence of a lagged symptom response for CFS score at that particular visit X.
- If there are at least half (50%) of the graphs show lagged symptom responses, we would conclude that dry eye symptoms (measured by SANDE questionnaire) show lagged response improvement in comparison to dry eye sign improvement.

For Period 2 analysis, Spearman correlation coefficient between change from baseline in CFS score at visit X and SANDE symptoms score at each visit X+i, its 95% confidence interval will be calculated by treatment group. The analysis will be based on the FAS Period 2 population.

For long term efficacy, the Entire Study analysis will be performed by repeating the Period 1 analysis for the entire 3 year duration using the FAS Entire Study population.

The analysis details are shown in Table 4 by study period.

Table 4 Analysis of Correlation between Change from Reference Point in CFS Score at Visit X and Change from Reference Point in SANDE Symptom Score at Visit X + i

Study Period / Analysis Population	Reference Point	Visit X	Visit X + i
Period 1 FAS Period 1 subjects	Baseline	Month 3*	Month 3, Month 6, Month 9, Month 12
		Month 6*	Month 6, Month 9, Month 12
		Month 9	Month 9, Month 12
		Month 12	Month 12
Period 2 FAS Period 2 subjects (by treatment arm)	Month 12	Month 15*	Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36
		Month 18*	Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36
		Month 21*	Month 21, Month 24, Month 27, Month 30, Month 33, Month 36
		Month 24*	Month 24, Month 27, Month 30, Month 33, Month 36
		Month 27*	Month 27, Month 30, Month 33, Month 36
		Month 30*	Month 30, Month 33, Month 36
		Month 33	Month 33, Month 36
		Month 36	Month 36

Study Period / Analysis Population	Reference Point	Visit X	Visit X + i
Entire Study (Period 1 + Period 2) FAS Entire Study subjects	Baseline	Month 3*	Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36
		Month 6*	Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36
		. . .	
		Month 27*	Month 27, Month 30, Month 33, Month 36
		Month 30*	Month 30, Month 33, Month 36
		Month 33	Month 33, Month 36
		Month 36	Month 36

* Spearman correlation coefficients will be plotted

8.1.2. Sensitivity Analysis

Sensitivity analyses will be performed by using the subjects in the PPS Period 1 population, the PPS Period 2 population, and the PPS Entire Study population respectively for the data from corresponding analysis period.

8.2. Analysis of Secondary Efficacy Endpoints

8.2.1. Analysis of Continuous Endpoints

The following secondary efficacy endpoints will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum by study period and visit. Also, Period 2 summaries will be done by the randomized treatment.

- CFS score and change from baseline at each visit for Period 1 and Entire Study, and change from Month 12 for each visit in Period 2. Shift tables that show the change from baseline (or Month 12) in CFS score as categorical variable will also be provided.
- Conjunctival fluorescein staining score (nasal, temporal, and total scores separately) and change from baseline at each visit for Period 1 and Entire Study, and change from Month 12 for each visit in Period 2. Shift tables for nasal and temporal conjunctival staining scores will be presented as well.

- SANDE symptoms score and change from baseline at each visit for Period 1 and Entire Study, and change from Month 12 for each visit in Period 2
- Symptoms score (5-point scale) and change from baseline at each visit, for each of the five symptoms assessed for Period 1 and Entire Study, and change from Month 12 for each visit in Period 2
- TBUT and change from baseline at each visit for Period 1 and Entire Study, and change from Month 12 for each visit in Period 2
- Schirmer test and change from baseline at Month 12 visit (Period 1), change from Month 12 visit at Month 24 and Month 36 visits (Period 2), and at each visit (Entire Study)
- Use of Artificial Tears over the last week (the average number of times per day and the number of days the artificial tears were used will be summarized separately) and change from baseline at each visit for Period 1 and Entire Study, and change from Month 12 for each visit in Period 2

In addition to descriptive statistics and shift table, mixed model for repeated measures (MMRM) will be applied to estimate the response of change from Month 12 for the following endpoints;

- CFS, Conjunctival fluorescein staining score, SANDE symptoms score, Symptoms score (5-point scale), TBUT, Schirmer test and Use of Artificial Tears over the last week.

In each endpoint, separate MMRM will be applied, and the analysis will be performed using observed case of each endpoint with the FAS population Period 2. Each model will include (randomized) treatment, visit, treatment by visit interaction as fixed effects, and the corresponding Month 12 value and geographic region (Europe vs. non-Europe) as covariates. Within-subject errors will be modeled using an unstructured (UN) covariance matrix. If there are convergence issues, covariance matrix structures other than unstructured will be tried in the following order: (1) heterogeneous Toeplitz (TOEPH), (2) heterogeneous autoregressive of order 1 (ARH(1)), (3) heterogeneous compound symmetry (CSH), and (4) compound symmetry (CS). The first covariance structure that converges will be used.

Least squares mean values for each treatment arm and the differences between least squares treatment arm means and associated 95% confidence intervals with t-distribution will be reported for each visit in addition nominal p-value.

8.2.2. Analysis of DEQS-15 Questionnaire

Dry Eye related Quality of life Score (DEQS) overall frequency score, overall degree score, and 1 item overall assessment of symptom will be summarized by visit. For these summary scores, the change from baseline will also be provided for the FAS Period 1, for the subjects who experienced marked improvement during Period 1, and for the FAS Period 2 Entire Study.

For subjects who are randomized in Period 2, the DEQS summary scores and change from Month 12 will be summarized at each visit by treatment group for data collected in Period 2 using the FAS Period 2 population.

To describe a long term effect of study treatment on the quality of life, the DEQS scores and change from baseline will be summarized for the entire 3 year period using the FAS Entire Study population.

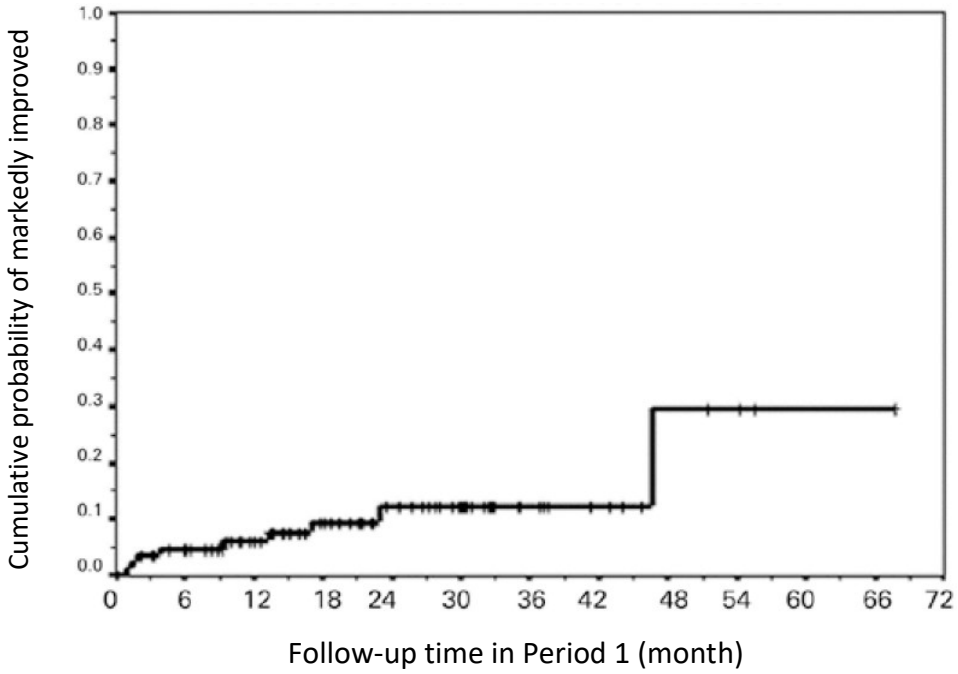
8.2.3. Analysis of Time-to-Event Endpoints

There are two time-to-event secondary efficacy endpoints in this study:

- Occurrence and time-to-become markedly improved (defined as CFS score improvement of 2 or more on the modified Oxford scale at post-baseline)
- Occurrence and time-to-relapse (increase of CFS score of 2 or more on the modified Oxford scale)

For each endpoint, the occurrence rate will be tabulated using frequency (n) and percent (%). The time-to-event data will be summarized by median time to event and its 95% confidence interval or minimum, median and maximum in case total number of events will not be enough. Survival functions will be presented graphically with the Kaplan-Meier curve (Kaplan et al., 1958) of event plot (failure plot).

Figure 3 Kaplan-Meier Curve of Time-to-become Markedly Improved



Time-to-become markedly improved will be analyzed using the FAS Period 1 population data.

Time-to-relapse will be analyzed by using the FAS Period 2 data. Median time-to-relapse, hazard ratio and 95% CI will be calculated from a Cox proportional hazards model with

geographic region (Europe vs. non-Europe) and treatment as factors, and CFS score at Month 12 in the study eye as a covariate.

8.2.4. Analysis of Others

To evaluate the magnitude of corneal cleanliness (complete resolution), proportion of subjects with 0 score of CFS will be summarized by treatment group at each visit for period 2 with FAS period 2. The number of subjects with 0 score of CFS, proportion (%) of subjects, difference of the proportion, the corresponding 95% confidence interval and p-value (Chi-square test) will be provided.

8.3. Subgroup Analyses

For period 1, the clinical subgroup of interest are

- Sjögren patients
- Subjects who experienced marked improvement during Period 1 where 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.

Efficacy analysis of Period 1 will be repeated using this subpopulation.

For Period 2, subgroup analysis by Sjögren patients will be conducted to investigate the treatment effects of the target population across region in Period 2. Other subgroup analyses may be performed as deemed necessary.

9. SAFETY ANALYSES

The safety-related measures collected in this study include AEs, intraocular pressure (IOP), best-corrected distance visual acuity (BCDVA), and slit-lamp biomicroscopy. All the safety-related measures will be summarized descriptively on the Safety population by study period and by actual treatment received (Period 2).

9.1. Analysis of Primary Safety Endpoint

The primary safety endpoint for this study is the incidence rate and time-to-onset of ocular surface complications, which include corneal ulceration, corneal perforation, loss of visual acuity, or ocular infection. Missing data will not be imputed.

The ocular surface complications incidence rate will be tabulated using frequency (n) and percentage (%) at Month 1-12, Month 13-24, Month 25-36 and for overall period 2 (Month 13-36). Month 1-12 incidence rate will be summarized for Period 1 Safety population. Month 13-

24, Month 25-36, and Month 13-36 (overall period 2) summaries will be conducted for Period 2 Safety population. The relative risk of the ocular surface complications incidence rate between the two treatment groups will be assessed at Month 13-24, Month 25-36 and Month 13-36 by producing odds ratio and its 2-sided 95% exact confidence interval.

For entire study analysis, the ocular surface complications incidence rate of IKERVIS group (a treatment group with IKERVIS during period) at Month 36 (1-36) will be compared to the existing epidemiologic rate in a comparable population, which was 4% based on results published by Petroutsos *et al*. (1992). The ocular surface complications incidence rate at Month 36 will be compared. This will be done using the Safety population Entire Study. Binomial proportions will be compared using SAS procedure PROC FREQ with binomial options.

The relative risk of the two treatment groups in terms of the time-to-first-onset of ocular surface complications (first event of each subject) will be assessed by producing the hazard ratio and its 2-sided 95% confidence interval if enough events are observed to make the analysis possible for period 2 (double masked period). The estimated hazard ratio and 95% CI will be obtained from a Cox proportional hazards model with treatment group as a covariate and region as stratification factor. Survival functions will be estimated using the Kaplan-Meier method, and Log-Rank test will be conducted to calculate nominal p-value.

9.2. Adverse Event

Subjects with any AE(s) will be tabulated by type of AE(s) by study period and for each actual treatment received and overall (Period 2 and Entire Study) for all AEs, ocular AEs, and non-ocular AEs separately. Unless otherwise specified, any AE experienced by either eye or both eyes will be counted once for that AE. In addition to the overall AE summary, subjects with any AE(s) will be tabulated by SOC and preferred term. A subject who experienced multiple AEs within a SOC or preferred term will be counted only once for that SOC or preferred term. SAEs, ADRs, serious ADRs will be tabulated similarly. Non-serious AEs (including number of events) and CSIs will also be summarized by SOC and preferred term.

AEs, SAEs, ADRs, serious ADRs, ocular AEs, AEs leading to death, AEs leading to study drug discontinuation, non-TEAEs, and CSIs, if any, will be listed separately.

9.3. Intraocular pressure (IOP)

Intraocular pressure (IOP) and its change from baseline (or change from Month 12) at each post-baseline visit will be summarized by study period and treatment (Period 2 and Entire Study) for study eyes and fellow eyes separately.

IOP scores and its change from baseline will be listed and records with IOP increase $\geq$ 10 mmHg at a particular visit will be flagged.

9.4. Best-Corrected Distance Visual Acuity (BCDVA)

Best-corrected distance visual acuity (converted in logMAR scale, see details in Table 2. Safety Assessments) and its change from baseline at each post-baseline visit will be summarized by study period and treatment (Period 2 and Entire Study) for study eyes and fellow eyes separately.

BCVA scores and its change from baseline will be listed and records with BCVA worsening of 3 lines or more (i.e., increase in logMAR score ≥ 0.3) at a particular visit will be flagged. Increase in logMAR scores means worsening in visual acuity.

9.5. 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, or 4=Very severe), rating scores and changes from baseline will be summarized by study period and analysis visit for study eyes and fellow eyes, separately.

For lashes (Normal or Abnormal) and lens (Aphakic, Pseudophakic, or Phakic), shift from baseline in status will be summarized by analysis visit for study eyes and fellow eyes, separately. For phakic eyes, cataracts severity will be summarized by study period and analysis visit. Any worsening in status from Normal at baseline to Abnormal after baseline in eye lashes will be listed.

Slit-lamp parameters at each visit will be listed. Subjects with any worsening of ≥ 2 units (except for lashes and lens) from baseline, or lashes changed from normal at baseline to abnormal post-baseline, or lens status change from phakic to pseudophakic or aphakic will be flagged.

9.6. Urine Pregnancy Test

Positive urine pregnancy test results will be listed.

10. CHANGES TO THE PROTOCOL-SPECIFIED ANALYSES

10.1. The Term "Study Eye"

The terms "analysis eye" and "study eye" were used interchangeably throughout the protocol. In this SAP the term "study eye" will be used throughout.

10.2. Primary Efficacy Endpoint

Primary Efficacy Endpoint

"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." was changed to "The correlation between 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."

Secondary Efficacy Endpoint

"Occurrence and time to become markedly improved (defined as CFS score improvement of 2 or more on the modified Oxford scale at Month 12)" was changed to " Occurrence and time to become markedly improved (defined as CFS score improvement of 2 or more on the modified Oxford scale)."

10.3. Descriptions of the 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 change from baseline in CFS score at visit X and symptoms score at each visit X+i will be summarised.

The protocol section 13.7 says "Mean and mean change from baseline (signs, symptoms and QOLs) will be provided. Correlation coefficient between 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".

Revised in this SAP: "Mean and mean change from baseline (signs, symptoms and QoL parameters) will be summarized. Correlation coefficient between change from baseline in CFS score at visit X and symptom score at each visit X+i will be calculated, where X includes scheduled visits from Month 3 to Month 12, and i is from 0 up to 3 (for Month 3, Month 6, Month 9, and Month 12, respectively)".

- Day 1 is changed to Month 3 for the starting visit of X because Day 1 would have no changes in any score.
- The ending number for i is changed from 4 to 3 due to one less visit.
- Added "(for Month 3, Month 6, Month 9, and Month 12, respectively)" to the end for clarification purpose.

10.4. Safety Population Definitions

Definitions for the Safety population for Period 2 and the entire study are updated in Section 6.

For Period 2 and Entire Study:

- The **FAS Period 2 (or FAS Entire Study)** population consists of all randomized subjects who received at least one dose of the double-masked 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 Period 2 (or PPS Entire Study)** will be a subset of FAS Period 2, 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 Period 2 (or Safety Population Entire Study)** consists of all subjects randomized in Period 2 who received at least one dose of the double-masked study medication and for whom any follow-up information is available in Period 2. It will be the analysis population for safety analyses to be performed with subjects as treated.
- The **Sjögren Patients Population** (**Period 2 or Entire Study)** consists of subjects who were known to have diagnostic status of the Sjögren disease based on the medical history obtained at baseline and satisfies FAS Period 2 or Safety Population Period2 criteria depending on analysis.

11. REFERENCES

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12. APPENDICES