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Cyclosporine 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting

Amended Protocol

Version 3.0

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Health Economics and Epidemiology

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Abbreviations

Abbreviation	Full description
ADR	Adverse drug reaction
AE	Adverse event
ATs	Artificial Tears
CAIs	Carbonic anhydrase inhibitors
CI	Confidence interval
EAS	Effectiveness analysis set
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
CFS	Corneal fluorescein staining
GPP	Good Pharmacoepidemiological Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoeconomics
SAE	Serious adverse event
SD	Standard deviation
SPC	Summary of product characteristics
TBUT	Tear break up time
VA	Visual acuity

1. Abstract

1.1. Title

Cyclosporine 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting.

1.2. Description of the medicinal product

Ikervis® is a 1mg/mL cyclosporine eye drops emulsion for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

1.3. Rationale and background

This is a prospective, non-interventional study of the effectiveness, tolerability and safety of Ikervis® in the targeted population as defined in section 1.6 of the SPC, in a real world setting.

1.4. Research objectives

The primary objective of this study is to assess the effectiveness of Ikervis® in controlling severe keratitis in adult patients with dry eye disease, as measured by corneal fluorescein staining (CFS) improvement from baseline to 12 months from treatment initiation, in Ikervis® naïve patients who have not improved despite treatment with tear substitutes, in routine clinical practice.

1.4.1. Primary endpoint

The primary endpoint is change in the grade of corneal fluorescein staining (CFS) from baseline to 12 months from initiation of Ikervis® treatment.

The baseline value will be collected and shall be measured only after obtaining informed consent and within 7 days before the start of Ikervis® treatment.

Endpoint data will be collected 12 months (± 45 days) from the initiation of Ikervis® treatment.

1.4.2. Key secondary endpoints

- Evaluation of subjective symptoms: foreign body sensation, burning/stinging, itching, pain, sticky feeling, blurred vision and photophobia
- Schirmer’s test without anaesthesia Optional
- Tear film breakup time (TFBUT). Optional

- Eyelid and conjunctival erythema
- Change in use of artificial tears
- Steroid tapering
- Mean change in Visual acuity (VA)
- Evaluation of the effectiveness of Ikervis® by the physician
- Evaluation of clinical signs during therapy with Ikervis® by the physician
- Evaluation of tolerability of Ikervis® by the physician
- Evaluation of tolerability of Ikervis® by the patient
- Concomitant therapy for keratitis and dry eye disease

1.5. Study design

- Non-interventional prospective study
- Decision to treat to be made according to routine clinical practice and by the treating physician
- 5 Visits:
    - Visit 1: Baseline visit within 7 days before the start of first Ikervis® prescription
    - Visit 2: Examination at 4 weeks (± 7 days) from the first Ikervis® prescription
    - Visit 3: Examination at 12 weeks (± 14 days) from the first Ikervis® prescription
    - Visit 4: Examination at 24 weeks (± 14 days) from the first Ikervis® prescription
    - Visit 5: Examination at 12 months (± 45 days) from the first Ikervis® prescription

1.6. Population

This study will include adult severe keratitis patients with dry eye disease, which has not improved despite treatment with tear substitutes, who received their first Ikervis® prescription at baseline, even if Ikervis® was not continued after the first prescription. In addition, patients must have their first prescription of Ikervis® within 7 days after their baseline CFS measure, in order to be eligible for this study. Only those who provide informed consent will be included.

At the time of a scheduled clinic visit, eligible patients will be invited to participate in the study and willing patients will be requested to sign an informed consent form. Once informed consent is obtained, the patient is included in the study and relevant data will be recorded during routine clinical visits. Participation in this study is entirely voluntary; any patient may withdraw consent to participate in this study at any time. The withdrawn patient's data will not be analysed in this study and the number of patients who withdrew consent will appear in the final study report.

1.6.1. Inclusion criteria

- Signed informed consent obtained before any study-related activities (study-related activities are any procedure related to the collection of data according to the protocol)

- Male or female 18 years of age and over
- Severe keratitis in patients with dry eye disease
- Currently on AT treatment
- Not used Ikervis® before

1.6.2. Exclusion criteria

- Patients currently, or within 6 months prior to baseline, using a cyclosporine ophthalmic preparation or tacrolimus or sirolimus
- Participation in other investigational drug or device study within 30 days prior to enrolment
- Participation in another clinical study at the same time as the present study. Such patients will be excluded from the effectiveness analysis
- Any ophthalmologic surgery within 6 months prior to the study
- Patient pregnant or nursing
- Pregnancy planned in the following 12 months
- Presence of contraindications as listed in the SPC

1.6.3. Minimum required data:

- CFS value within 7 days prior to date of first Ikervis® prescription
- CFS value at 12 months (±45 days) after the date of first Ikervis® prescription

1.7. Variables

Where appropriate, variables will be recorded for each eye separately.

1.7.1. Baseline visit

- Demographic data
  - Gender
  - Date of birth
- Type of prior treatment and duration of use (both topical and systemic)
- CFS at baseline (Oxford scale grade)
  - 0
  - I

  - II
  - III
  - IV
  - V
- Evaluation of subjective symptoms under prior treatment.
  Severity categorised as none, mild, moderate, severe.
  - foreign body sensation
  - burning/stinging
  - itching
  - pain
  - sticky feeling
  - blurred vision
  - photophobia
- Evaluation of clinical signs under prior treatment
  - Schirmer's test without anaesthesia. Optional
  - Tear break up time (TBUT). Optional
  - Eyelid erythema
    - None
    - Mild
    - Moderate
    - Severe
  - Conjunctival erythema
    - None
    - Mild
    - Moderate
    - Severe
- Visual acuity test
- Use of artificial tears
  - Number of drugs
  - Frequency of use
- Reason(s) for change of medical therapy (effectiveness evaluation of prior treatment)
  - Insufficient keratitis / dry eye disease control with prior medication

  - Progression of keratitis / dry eye disease
  - Poor local tolerance
  - Poor compliance
  - Other reasons
- Any systemic disease
- Systemic therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication
- Topical ocular therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication
  - Adverse events during the study

1.7.2. Visits at 4 weeks (±7 days), 12 weeks (±14 days), 24 weeks (±14 days) and 12 months (±45 days) post first Ikervis® prescription

- CFS at current visit: (Oxford scale grade)
  - 0
  - I
  - II
  - III
  - IV
  - V
- Evaluation of subjective symptoms under prior treatment
  Severity categorised as none, mild, moderate, severe.
  - foreign body sensation
  - burning/stinging
  - itching
  - pain

  - sticky feeling
  - blurred vision
  - photophobia
- Evaluation of clinical signs under Ikervis® treatment
  - Schirmer's test without anaesthesia. Optional
  - Tear break up time (TBUT) Optional
  - Eyelid erythema
    - None
    - Mild
    - Moderate
    - Severe
  - Conjunctival erythema
    - None
    - Mild
    - Moderate
    - Severe
- Visual acuity test
- Use of artificial tears
  - Number of drugs
  - Frequency of use
- Reason(s) for discontinuation of Ikervis®, if applicable
  - Insufficient keratitis / dry eye disease control with prior medication
  - Progression of keratitis / dry eye disease
  - Poor local tolerance
  - Poor compliance
  - Other reasons
- Systemic therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication

- Topical ocular therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication
- Documentation of adverse events during the study

1.8. Data sources

Once an informed consent form is signed by the patient, the patient is enrolled in the study and site staff may enter data into the electronic case report form (eCRF) covering the first visit. The date of Ikervis® initiation must subsequently be recorded in the eCRF.

During routine visits at 4 weeks (±7 days), 12 weeks (±14 days), 24 weeks (±14 days) and 12 months (±45 days) post first Ikervis® prescription, site staff will enter data relating to these visits into the eCRF. Only data elicited as part of standard care will be entered into the eCRF.

1.9. Study size

The planned enrolment target is approximately 400 patients from study sites in five countries.

1.10. Data analysis

The primary analysis will be a comparison of the grade of CFS at baseline with that at 12 months after Ikervis® initiation. Where data on both eyes is available, both will be recorded and the CFS assessment for the worst eye at baseline used in the analysis, defined as the eye with the worst CFS grade at baseline. If both eyes have the same CFS grade then data from the right eye will be used. As such, the full analysis set will include all patients who received at least one prescription of Ikervis®. Analysis of secondary endpoints and sub-group analysis will be conducted and presented as outlined in section 5.7. All analyses will be further described in the statistical analysis plan.

A complete-case analysis approach will be undertaken for all analyses. The amount of missing information will be summarised and assessed; if more than 15% of patients have missing data for a particular outcome, patient characteristics will be compared for those with and those without missing information to assess generalizability of the findings. All tests of statistical significance will be two-sided and will be assessed at a significance level of 5%.

2. Rationale and background

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a multifactorial, chronic and progressive ophthalmic disease causing inflammation and damage to the ocular surface, caused in part by increased osmolarity of the tear film.[1 2] DED is a disorder of the lacrimal glands, the entire ocular surface (cornea, conjunctiva and meibomian glands), and the eye lids, as well as the sensory and motor nerves that connect them.[3] Symptoms include discomfort, visual morbidity or disturbance, and tear film instability.[1 4] The symptoms of DED usually correlate poorly with the objective clinical findings such as corneal erosion, punctate keratopathy, epithelial defects, corneal ulceration (sterile or infected), corneal neovascularisation, corneal scarring, or even corneal perforation.[5-8] DED is usually chronic, and no specific cure exists.

Complications associated with DED include conjunctivitis, corneal ulceration, and corneal infection [9]. DED may also compromise results of corneal, cataract or refractive surgery.[10] For patients with severe keratitis, treatment is mandatory to avoid the long term consequences of inflammation including ulceration and perforation which may lead to visual impairment and damage to corneal nerves through disease progression.[11]

Dysfunction of the ocular surface and the tear-secreting Meibomian gland, that usually maintain the tear supply and clear used tears, result in an unstable and poorly maintained tear film causing ocular signs and symptoms described above.[12] Subsequent dysregulation of native immune mechanisms leads to a cycle of continued inflammation, accompanied by changes in immune responses which characterize the chronicity of the condition as such, chronic inflammation is proposed as the core mechanism in the development and intensification of DED. [2 13 14]

Treatment depends on disease severity. Currently available medical options include artificial tear products, lubricants, topical steroids and cyclosporine A (CsA). Lubricants are classified as ‘health products’, proof of their efficacy is not required by Health Authorities [15], and many are available over-the-counter. Mild to moderate DED can usually be treated symptomatically with tear substitutes, but few effective treatments exist for moderate to severe DED. Artificial tears provide short-term relief at best, and require frequent dosing. The preservative (benzalkonium chloride) in many artificial tears often causes eye irritation. Clinical guidelines recommend using CsA as early as possible to avoid keratitis.[1 9]Any potential for symptomatic improvement provided by topical steroids should be considered alongside their known ocular side effects, including glaucoma and cataract.[16-18]

NOVA22007 1mg/ml is a new eye drop emulsion to treat severe keratitis in adult patients with DED. The current tradename is IKERVIS®. CsA is a lipophilic cyclic polypeptide that has been used for several decades as a systemic immunosuppressant and has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor (TCGF). It is also known to up-regulate the release of anti-inflammatory cytokines. Furthermore, hospital pharmacy compounded ophthalmic CsA is already widely used in clinical practice across Europe.

Two trials (SICCANOVE and SANSIKA) compared Ikervis® efficacy on keratitis compared to vehicle at 6 months. SANSIKA was performed in DED patients with severe keratitis; while SICCANOVE included DED patients with moderate to severe keratitis (17% at baseline had severe keratitis). In both studies, symptoms markedly improved over time in both groups. The two trials demonstrate improvement in the objective endpoint of corneal fluorescein staining (CFS) with Ikervis®, indicating a clinically relevant

therapeutic benefit in comparison to vehicle treatment. In SICCANOVE, the between groups difference in change in CFS from baseline (-0.22; 95% CI: -0.39, -0.06) was statistically significant (p=0.009) at 6 months in favour of the Ikervis® group. In SANSIKA, CFS-OSDI responder rate (the composite primary endpoint) at month 6 showed greater improvement (+5.5 points) in the Ikervis® group (44 patients, 28.6%) than in the vehicle group (21 patients, 23.1%), but this did not reach statistical significance. Analysis of CFS as a secondary endpoint showed significant improvement of corneal staining over time at Month 6 (p= 0.037). The incidence of ocular adverse events was higher in the Ikervis® group than the vehicle group in SICCANOVE (42.6% vs 26.8%) and in SANSIKA (37.0% vs 20.0%); most were mild to moderate and there was only one serious ocular AE.

At completion of the SANSIKA study (12 month study), patients were asked to enter the Post SANSIKA study. This study was an open-label, non-randomized, one-arm, 24-month study extension of the SANSIKA Study. In Post SANSIKA study patients alternatively received Ikervis® treatment or no treatment depending on CFS score (patients received Ikervis® when there was a worsening of keratitis).

This study was designed to monitor the long-term efficacy and relapse rates in patients who have previously received Ikervis®.

The primary objective of the study was to assess the duration of the improvement following Ikervis® treatment discontinuation once the patient was improved with respect to the baseline of the SANSIKA study (i.e. at least 2 grade improvement on the modified Oxford scale).

67 patients were enrolled (37.9% of the 177 patients having ended SANSIKA). After the 24-month period, 61.3% of 62 patients included in the primary efficacy population did not experience a relapse based on CFS scores. Percentage of patients who experienced a severe keratitis recurrence was 35% and 48% in patients treated 12 months and 6 months with Ikervis® respectively in the SANSIKA study.

Based on the first quartile (the median could not be estimated due to the small number of relapses), time to relapse (back to CFS grade 4) was ≤224 days and ≤175 days in patients previously treated 12 months and 6 months with Ikervis®, respectively. Patients spent more time on CFS grade 2 (Median 12.7 weeks/year) and grade 1 (Median 6.6 weeks/year) than CFS grade 3 (Median 2.4 weeks/year), CFS grades 4 and 5 (Median time 0 week/year).

Assessment of DED symptoms by VAS showed a worsening of patient's discomfort from the time treatment was first stopped to the time it was restarted except pain which remained relatively low and stable. The median global VAS score increased from the time treatment was first stopped (23.3%) to the time treatment was restarted (45.1%).

No significant changes have been observed in the other secondary endpoints (TBUT, lissamine green staining and Schirmer test, NEI-VFQ and EQ-5D) over the course of the extension study.

The results of the Phase III programme demonstrate that compared to vehicle, once daily Ikervis® provides a clear and sustained significant improvement of corneal staining, a significant reduction in ocular surface inflammation and a significant improvement in tear osmolarity. Ikervis® also has a beneficial effect on symptoms. These eye-health benefits of Ikervis® are important to clinicians who are interested in maintaining the integrity of the ocular surface knowing that in patients with DED, increased ocular surface disease usually correlates with reduced corneal sensation, and severe keratitis can lead to major ocular complications, such as infections, ulcers or corneal perforation with irreversible loss of visual acuity [19 20].

Severe keratitis is the main concern for ophthalmologists since it can lead to corneal ulceration and impaired vision. Therefore, treating severe keratitis and maintaining and protecting the integrity of the ocular surface is an important clinical challenge.

The efficacy Ikervis® has been explored in trials however there is a lack of evidence from the real-world, observational setting. This non-interventional prospective study will evaluate the effectiveness, tolerability and safety of Ikervis® in routine clinical practice. As such, the study will recruit a substantially more heterogeneous patient population than would be seen in a clinical trial.

3. Research question and background

3.1. Primary objective

The primary objective of this study is to assess the effectiveness of Ikervis® in controlling severe keratitis, as measured by corneal fluorescein staining (CFS) improvement from baseline to 12 months (± 45 days) from treatment initiation, in patients who have not improved despite treatment with tear substitutes, in routine clinical practice

3.2. Secondary objectives

- To assess the following
  - foreign body sensation
  - burning/stinging
  - itching
  - pain
  - sticky feeling
  - blurred vision
  - photophobia
- To assess tear production using Schirmer's test without anaesthesia
- To assess tear film breakup time (TFBUT)
- To evaluate eyelid and conjunctival erythema
- Quantify reductions in the use of artificial tears
- To quantify steroid tapering

4. Workflow and data collection

After confirming a centre's participation by signing the agreement to participate in this non-interventional study, all participating centres will receive the required documents from Santen. The collection of patient data is possible as soon as the participants have received the documents of the non-interventional study.

Each participating centre takes sole responsibility for the correct and complete documentation of all data collected at their own centre.

5. Research methods

5.1. Study design

This is a non-interventional prospective study collecting data during routine clinical visits by adult patients with dry eye disease and severe keratitis which has not improved despite treatment with tear substitutes.

Baseline data would be collected at the point the patient consents to participate in the study and before the initiation of Ikervis® therapy. For inclusion in the analysis, Ikervis® therapy should have been initiated within 7 days after the collection of baseline data.

Corneal fluorescein staining measured at baseline and after 4 weeks (± 7 days), 12 weeks (± 14 days) and 24 weeks (±14 days) and after 12 months (± 45 days) post initiation of Ikervis® therapy will be recorded, irrespective of whether or not the patient was still on Ikervis® treatment at the time of the visit. Each patient's CFS data at each follow up visit will be compared with the same patient's data at baseline, thereby having each patient act as their own control.

The objective of this study is to understand the effectiveness of Ikervis® in routine clinical practice. To achieve this objective, it is important to collect real-world data from patients, not from within a controlled environment as is typically the case in randomised clinical trials. A prospective non-interventional study was selected as the appropriate study design.

Data on each patient will be entered directly into an electronic case report form at each consultation to capture information within 7 days before the initiation of Ikervis® therapy and after 12 months (± 45 days) of the initiation of Ikervis® therapy.

5.1.1. Primary endpoint

The primary endpoint is change (+, 0, -) in the grade of corneal fluorescein staining (CFS) from baseline to 12 months from initiation of Ikervis® treatment.

The baseline value will be collected and shall be measured only after obtaining informed consent and within 7 days before the start of Ikervis® treatment.

Endpoint data will be collected 12 months (± 45 days) from the initiation of Ikervis® treatment

The primary endpoint will be assessed for the whole patient group and separately in specific subgroups (Previous steroid user / non users).

5.1.2. Secondary endpoints

- Change in the severity of subjective symptoms
  - foreign body sensation
  - burning/stinging

  - itching
  - pain
  - sticky feeling
  - blurred vision
  - photophobia
- Mean change in Schirmer's test without anaesthesia. Optional
- Mean change in tear break up time (TBUT). Optional
- Change in eyelid erythema distribution by severity
  - None
  - Mild
  - Moderate
  - Severe
- Change in conjunctival erythema distribution by severity
  - None
  - Mild
  - Moderate
  - Severe
- Change in the use of artificial tears
  - Reduction in the number and frequency of artificial tears
- Steroidal tapering
  - Proportion of patients initially prescribed steroids with Ikervis®, or already prescribed steroids when Ikervis® was prescribed
  - Mean duration of steroid use by
    - initial dose
    - change in dose (initial – final)
    - Continuing / stopped steroid use

- Mean change in Visual acuity (VA)
- Evaluation of the effectiveness of Ikervis® by the physician
  - Better than prior medication
  - Same as prior medication
  - Worse than prior medication

- Evaluation of clinical signs during therapy with Ikervis® by the physician
  - Better than prior medication
  - Same as prior medication
  - Worse than prior medication
- Evaluation of tolerability of Ikervis® by the physician
  - Very good
  - Good
  - Satisfactorily
  - Poor
- Evaluation of tolerability of Ikervis® by the Patient
  - Very good
  - Good
  - Satisfactorily
  - Poor
- Concomitant therapy for keratitis and dry eye disease

All secondary endpoints will be assessed for the whole patient group and separately in specific subgroups (Previous steroid user / non users).

5.1.3. Treatment of patients

The patient's physician is solely responsible for the initiation of treatment, following the specifications set out in the SPC for Ikervis®, and for the consideration of precautions, contraindications and all other details of the treatment.

Participation in this non-interventional study does not have any influence on the prescription or number of prescriptions of Ikervis® nor on those of any other treatment.

5.1.3.1. Dosage

One drop of Ikervis® per day once daily to be applied to the affected eye(s) at bedtime, as outlined in the SPC.

5.1.3.2. Duration of use

The duration of use for an individual patient is determined by their therapeutic requirements as assessed by their attending physician.

5.1.3.3. Concomitant medications

During this non-interventional study it is possible that other concomitant medications may be prescribed by a patient's physician, according to the specifications of the SPC. If concomitant medications are needed these should be recorded in the eCRF.

5.1.3.4. Documentation of medication

The following details must be specified in the eCRF:

- Starting date of medical treatment with Ikervis®
-
- Prior and concomitant medication , indication, duration and dosage

5.2. Setting

Data will be recorded during routine consultations by adults with severe keratitis in dry eye disease, who received their first Ikervis® prescription, at clinics in Germany, the United Kingdom, Sweden, Norway and Finland.

In this prospective study, patient eligibility will be determined by their attending physician, according to the inclusion and exclusion criteria set out in this protocol. Eligible patients attending an appointment at a participating clinic will be informed of the study. Patients who provide informed consent will be included in the study. During routine consultations with their physician clinical information will be recorded in the eCRF. The target population for the current study is all eligible patients who received at least one prescription of Ikervis® in Germany, the United Kingdom, Sweden, Norway and Finland; however the sample population will be limited to eligible patients in the clinics included in the study.

5.2.1. Study population

Planned number of patients to be included: approximately 400

Planned number of patients to be included in the primary analysis: approximately 400

5.2.2. Inclusion criteria

- Signed informed consent obtained before any study-related activities (study-related activities are any procedure related to the collection of data according to the protocol)
- Male or female 18 years of age and over
- Severe keratitis in patients with dry eye disease
- Currently on AT treatment
- Not used Ikervis® before

5.2.3. Exclusion criteria

- Patients currently, or within 6 months prior to baseline, using a cyclosporine ophthalmic preparation or tacrolimus or sirolimus
- Participation in other investigational drug or device study within 30 days prior to enrolment
- Participation in another clinical study at the same time as the present study. Such patients will be excluded from the effectiveness analysis
- Any ophthalmologic surgery within 6 months prior to the study
- Patient pregnant or nursing
- Pregnancy planned in the following 12 months
- Presence of contraindications as listed in the SPC

5.2.4. Minimum required data:

- CFS value within 7 days prior to date of first Ikervis® prescription
- CFS value at 12 months (±45 days) after the date of first Ikervis® prescription

5.2.5. Withdrawal criteria

The patient may withdraw consent at any time. If a patient decides to withdraw consent, no additional data will be recorded. The withdrawn patient's data will not be analysed in this study and the number of patients who withdrew consent will appear in the final study report.

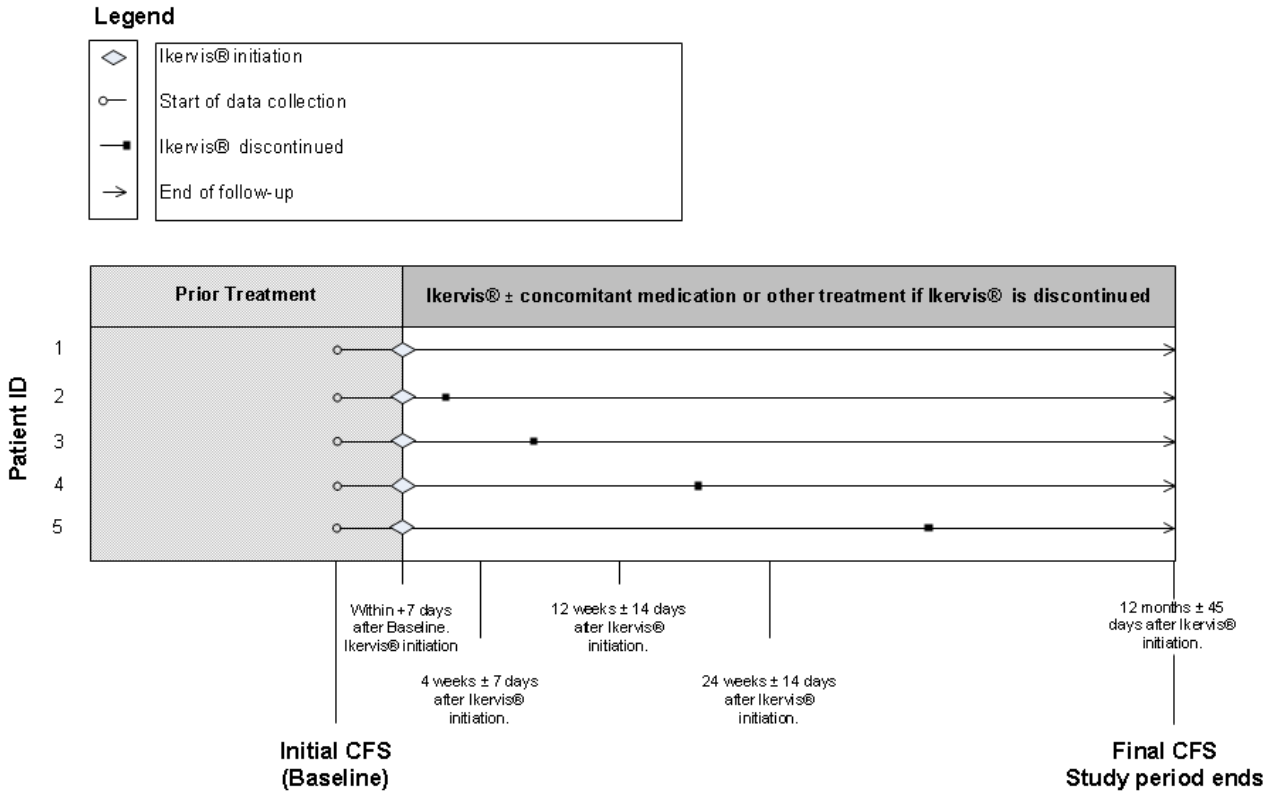
5.2.6. Rationale for selection criteria

The present study population constitutes a broader real-world adult patient population with severe keratitis in dry eye disease than is typically included in randomised controlled trials. This study seeks to represent the current patient population treated with Ikervis® in the real-world setting, and their associated treatment patterns.

5.2.7. Visit procedure

The study accrual period will be determined based on the number of clinics recruited to achieve the current study goals. Collection of data for eligible patients will be undertaken between approximately March 2017 and November 2019, assuming a sufficient number of clinics to provide data for approximately 400 patients. During the recruitment period all eligible patients attending participating clinics will be invited to participate in the study, and if patients provide informed consent, relevant data will be recorded during routine clinical visits.

The flow chart below shows the time points at which data will be collected.



For definitions of 'baseline' refer to section 5.1.1. The variables to be collected at each time point are outlined in section 5.3. Country and site information will be collected for all participants.

5.3. Variables

Country and site information will be collected for all participants. Where appropriate, variables will be recorded for each eye separately.

5.3.1. Baseline visit

- Demographic data
  - Gender
  - Date of birth
- Type of prior treatment and duration of use (both topical and systemic)
- CFS at baseline (Oxford scale grade)
  - 0

  - I
  - II
  - III
  - IV
  - V
- Evaluation of subjective symptoms under prior treatment.
  Severity categorised as none, mild, moderate, severe.
  - foreign body sensation
  - burning/stinging
  - itching
  - pain
  - sticky feeling
  - blurred vision
  - photophobia
- Evaluation of clinical signs under prior treatment
  - Schirmer's test without anaesthesia. Optional
  - Tear break up time (TBUT). Optional
  - Eyelid erythema
    - None
    - Mild
    - Moderate
    - Severe
  - Conjunctival erythema
    - None
    - Mild
    - Moderate
    - Severe
- Visual acuity test
- Use of artificial tears
  - Number of drugs
  - Frequency of use
- Reason(s) for change of medical therapy (effectiveness evaluation of prior treatment)

  - Insufficient keratitis / dry eye disease control with prior medication
  - Progression of keratitis / dry eye disease
  - Poor local tolerance
  - Poor compliance
  - Other reasons
- Any systemic disease
- Systemic therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication
- Topical ocular therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication
- Adverse events during the study

5.3.2. Visits at 4 weeks (± 7 days), 12 weeks (±14 days), 24 weeks (±14 days) and 12 months (±45 days) post first Ikervis® prescription

- CFS at current visit: (Oxford scale grade)
  - 0
  - I
  - II
  - III
  - IV
  - V
- Evaluation of subjective symptoms under prior treatment
  Severity categorised as none, mild, moderate, severe.
  - foreign body sensation
  - burning/stinging
  - itching

  - pain
  - sticky feeling
  - blurred vision
  - photophobia
- Evaluation of clinical signs under Ikervis® treatment
  - Schirmer's test without anaesthesia. Optional
  - Tear break up time (TBUT) Optional
  - Eyelid erythema
    - None
    - Mild
    - Moderate
    - Severe
  - Conjunctival erythema
    - None
    - Mild
    - Moderate
    - Severe
- Visual acuity test
- Use of artificial tears
  - Number of drugs
  - Frequency of use
- Reason(s) for discontinuation of Ikervis®, if applicable
  - Insufficient keratitis / dry eye disease control with prior medication
  - Progression of keratitis / dry eye disease
  - Poor local tolerance
  - Poor compliance
  - Other reasons
- Systemic therapies
  - Yes / No
  - Name
  - Dose and duration of use

  - Indication
- Topical ocular therapies
  - Yes / No
  - Name
  - Dose and duration of use
  - Indication
- Documentation of adverse events during the study

5.4. Data sources

All data collected within the study period shall be entered into the electronic case report forms provided by the sponsor. The data entry should be done for each patient soon after their clinical consultation. Data entry may be delegated by the participating physician to appropriately qualified and trained office staff. Data must be entered directly into the original paginated case report forms. The use of copies of these eCRFs is not permitted.

Corrections to the case report forms can be made at any time until the submission of the documents. In these cases it is mandatory that records are clear and legible. Please note also who has made the correction to the data.

5.5. Study size

This is an observational study, carried out with the objective of assessing the effectiveness of Ikervis® in controlling severe keratitis, as measured by corneal fluorescein staining (CFS) improvement from baseline to 12 months from treatment initiation, in patients who have not improved despite treatment with tear substitutes, in routine clinical practice.

As such, the study is not setting out to test any specific hypothesis, but rather to be hypothesis generating. Consequently, the sample size information provided here is offered in order to provide an approximate indication of the number of patients required in order to estimate the proportion of patients achieving a 1, 2 or 3 grade improvement in the primary outcome, i.e. their CFS score (the response rate), as measured on the Oxford grading scale, at 12 months (+/- 45 days) from baseline.

The largest sample size required to achieve a specified margin of error around the estimated proportion achieving a particular number of grades improvement will always occur if 50% of the population achieve this level. The required sample size reduces at higher or lower response rates (Figure 1).

Sample size				CFS >= 3 grades improvement																								CFS >= 2 grades improvement				
		Response																														
Margin of error	CI	40%	41%	42%	43%	44%	45%	46%	47%	48%	49%	50%	51%	52%	53%	54%	55%	56%	57%	58%	59%	60%	61%	62%	63%	64%	65%	66%	67%	68%	69%	70%
7.00%	0.14	636	641	645	649	653	656	658	660	661	662	662	662	661	660	658	656	653	649	645	641	636	630	624	617	610	603	594	586	576	567	556
7.05%	0.141	627	632	636	640	643	646	649	650	652	653	653	653	652	650	649	646	643	640	636	632	627	621	615	609	602	594	586	577	568	559	548
7.10%	0.142	618	623	627	631	634	637	639	641	643	643	644	643	643	641	639	637	634	631	627	623	618	612	607	600	593	586	578	569	560	551	541
7.15%	0.143	609	614	618	622	626	628	631	632	634	634	635	634	634	632	631	628	626	622	618	614	609	604	598	592	585	578	570	561	552	543	533
7.20%	0.144	601	606	610	614	617	620	622	624	625	626	626	626	625	624	622	620	617	614	610	606	601	596	590	584	577	570	562	554	545	535	526
7.25%	0.145	593	597	601	605	608	611	613	615	616	617	617	617	616	615	613	611	608	605	601	597	593	587	582	576	569	562	554	546	537	528	518
7.30%	0.146	584	589	593	597	600	603	605	607	608	609	609	609	608	607	605	603	600	597	593	589	584	579	574	568	561	554	546	538	530	521	511
7.35%	0.147	577	581	585	589	592	595	597	598	600	600	601	600	600	598	597	595	592	589	585	581	577	572	566	560	553	547	539	531	523	514	504
7.40%	0.148	569	573	577	581	584	587	589	590	592	592	592	592	592	590	589	587	584	581	577	573	569	564	558	552	546	539	532	524	516	507	498
7.45%	0.149	561	566	570	573	576	579	581	582	584	584	585	584	584	582	581	579	576	573	570	566	561	556	551	545	539	532	525	517	509	500	491
7.50%	0.15	554	558	562	565	568	571	573	575	576	577	577	577	576	575	573	571	568	565	562	558	554	549	544	538	532	525	518	510	502	494	485
7.55%	0.151	546	551	555	558	561	563	566	567	568	569	569	569	568	567	566	563	561	558	555	551	546	542	536	531	525	518	511	503	495	487	478
7.60%	0.152	539	544	547	551	554	556	558	560	561	561	562	561	561	560	558	556	554	551	547	544	539	535	529	524	518	511	504	497	489	481	472
7.65%	0.153	532	536	540	544	546	549	551	552	554	554	554	554	554	552	551	549	546	544	540	536	532	528	522	517	511	505	498	490	483	474	466
7.70%	0.154	525	529	533	536	539	542	544	545	546	547	547	547	546	545	544	542	539	536	533	529	525	521	516	510	504	498	491	484	476	468	460
7.75%	0.155	519	523	526	530	532	535	537	538	539	540	540	540	539	538	537	535	532	530	526	523	519	514	509	504	498	492	485	478	470	462	454
7.80%	0.156	512	516	520	523	526	528	530	531	532	533	533	533	532	531	530	528	526	523	520	516	512	507	503	497	491	485	479	472	464	456	448
7.85%	0.157	505	509	513	516	519	521	523	525	526	526	527	526	526	525	523	521	519	516	513	509	505	501	496	491	485	479	473	466	458	450	442
7.90%	0.158	499	503	507	510	512	515	517	518	519	520	520	520	519	518	517	515	512	510	507	503	499	495	490	485	479	473	467	460	452	445	437
7.95%	0.159	493	497	500	503	506	508	510	511	513	513	513	513	513	511	510	508	506	503	500	497	493	489	484	479	473	467	461	454	447	439	431
8.00%	0.16	487	491	494	497	500	502	504	505	506	507	507	507	506	505	504	502	500	497	494	491	487	482	478	473	467	461	455	448	441	434	426
8.05%	0.161	481	484	488	491	493	496	497	499	500	500	501	500	500	499	497	496	493	491	488	484	481	476	472	467	461	456	449	443	436	428	421
8.10%	0.162	475	478	482	485	487	490	491	493	494	494	495	494	494	493	491	490	487	485	482	478	475	471	466	461	456	450	444	437	430	423	415
8.15%	0.163	469	473	476	479	481	484	485	487	488	488	488	488	488	487	485	484	481	479	476	473	469	465	460	455	450	444	438	432	425	418	410
8.20%	0.164	463	467	470	473	476	478	479	481	482	482	483	482	482	481	479	478	476	473	470	467	463	459	455	450	445	439	433	427	420	413	405
8.25%	0.165	458	461	464	467	470	472	474	475	476	476	477	476	476	475	474	472	470	467	464	461	458	454	449	444	439	434	428	422	415	408	400
8.30%	0.166	452	456	459	462	464	466	468	469	470	471	471	471	470	469	468	466	464	462	459	456	452	448	444	439	434	429	423	417	410	403	396
8.35%	0.167	447	450	453	456	459	461	462	464	465	465	465	465	465	464	462	461	459	456	453	450	447	443	439	434	429	423	418	412	405	398	391
8.40%	0.168	441	445	448	451	453	455	457	458	459	460	460	460	459	458	457	455	453	451	448	445	441	438	433	429	424	418	413	407	400	393	386
8.45%	0.169	436	440	443	445	448	450	451	453	454	454	454	454	454	453	451	450	448	445	443	440	436	432	428	424	419	413	408	402	396	389	382
8.50%	0.17	431	435	438	440	443	445	446	447	448	449	449	449	448	447	446	445	443	440	438	435	431	427	423	419	414	409	403	397	391	384	377
8.55%	0.171	426	429	432	435	437	439	441	442	443	444	444	444	443	442	441	439	437	435	432	429	426	422	418	414	409	404	398	393	386	380	373
8.60%	0.172	421	424	427	430	432	434	436	437	438	439	439	439	438	437	436	434	432	430	427	424	421	417	413	409	404	399	394	388	382	375	368
8.65%	0.173	416	420	423	425	427	429	431	432	433	433	434	433	433	432	431	429	427	425	423	420	416	413	409	404	400	395	389	383	377	371	364
8.70%	0.174	412	415	418	420	422	424	426	427	428	428	429	428	428	427	426	424	422	420	418	415	412	408	404	400	395	390	385	379	373	367	360
8.75%	0.175	407	410	413	415	418	420	421	422	423	424	424	424	423	422	421	420	418	415	413	410	407	403	399	395	391	386	380	375	369	363	356
8.80%	0.176	402	405	408	411	413	415	416	417	418	419	419	419	418	417	416	415	413	411	408	405	402	399	395	391	386	381	376	371	365	358	352
8.85%	0.177	398	401	404	406	408	410	412	413	414	414	414	414	414	413	412	410	408	406	404	401	398	394	390	386	382	377	372	366	361	354	348
8.90%	0.178	393	396	399	402	404	406	407	408	409	409	410	409	409	408	407	406	404	402	399	396	393	390	386	382	377	373	368	362	357	350	344
8.95%	0.179	389	392	395	397	399	401	402	404	404	405	405	405	404	404	402	401	399	397	395	392	389	385	382	378	373	369	364	358	353	347	340
9.00%	0.18	385	388	390	393	395	397	398	399	400	400	401	400	400	399	398	397	395	393	390	388	385	381	377	373	369	365	360	354	349	343	336
9.05%	0.181	380	383	386	388	390	392	394	395	396	396	396	396	396	395	394	392	390	388	386	383	380	377	373	369	365	360	356	350	345	339	333
9.10%	0.182	376	379	382	384	386	388	389	390	391	392	392	392	391	390	389	388	386	384	382	379	376	373	369	365	361	357	352	347	341	335	329
9.15%	0.183	372	375	378	380	382	384	385	386	387	387	388	387	387	386	385	384	382	380	378	375	372	369	365	361	357	353	348	343	337	332	326
9.20%	0.184	368	371	374	376	378	379	381	382	383	383	383	383	383	382	381	379	378	376	374	371	368	365	361	357	353	349	344	339	334	328	322

Figure 1. Sample size required to estimate a range of response rates, with the specified margin of error and corresponding confidence interval (CI).

From the SANSIKA study (Baudouin et al. Eur J Ophthalmol 2017; 27(6): 678-685), the proportion of patients experiencing an improvement in CFS response of $\geq$ 2 grades or ≥ 3 following 12 months of treatment with 0.1% cyclosporine A cationic emulsion has previously been showed to be 66% and 42% respectively.

Based on market research data it is assumed that 60% of patients would previously have been on steroid treatment.

Based on former experience with observational studies it is assumed that 26% of patient records are dropped as a result of inconsistencies data.

Then in order to be able to estimate the proportion of patients responding with a 1+, 2+ or 3+ grade improvement, with approximately a 9% margin of error around each estimate, the planned enrolment target is approximately 400 patients to cover all potential response rates.

5.6. Data management

The physician must keep a patient enrolment log to record eligible patients providing informed consent to participate, and a log of patients evaluated for but not included in the study. These can be combined in one

document. Patient identification numbers can be assigned in a consecutive manner, with the first two digits of a patient's identification being the site identification, and the last digit(s) being the patient number (e.g., 04 – 25).

Data collected during scheduled consultations will be entered into an eCRF (DataTrak) and will be stored on their secured server. Each patient will be assigned a unique study identifier by the principal physician or designee, and there will be no direct identifiers attached to the recorded data. Only those assigned to the task of collecting data at each site will have access to the identified data. Physicians and all site staff participating in this study will be trained on study procedures prior to start of the study.

Appropriate measures such as encryption of data files must be used to assure confidentiality of patient data if it is transmitted over open networks.

ICON will provide electronic eCRFs for capture of study specific patient data. Instructions for completion and correction of eCRFs will be provided.

The physician must ensure that study specific patient data is entered in the eCRF according to agreed study specific timelines. The eCRFs data will be collected, by ICON.

The system for Electronic Data Capture (EDC), DataTrak, and support services for the system will be supplied by ICON.

An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for any correction, the original entry and the corrected entry.

By signing the affirmation statement/casebook the physician confirms that the information in the eCRF is complete and correct.

If corrections are made by the physician's authorised staff after the date of the physician's signature on the affirmation statement/casebook, this must be checked and signed again by the physician.

5.7. Data analysis

Wilcoxon signed rank test or sign test

5.7.1. Definition of analysis sets

The primary dataset will be the full analysis set (FAS) i.e. all patients having signed the informed consent form and for whom Ikervis® was prescribed at least once, irrespective of whether patients continued Ikervis® after the first prescription.

Any one analysis will include patient records with complete data on the variables required for that analysis. To reflect real life utilisation, no patient will be excluded from the follow up and analyses will start with the full cohort (regardless of continuation/discontinuation).

A secondary effectiveness analysis set (EAS) will include all patients already included in the FAS and having continued Ikervis® treatment for 12 months after initiation and with at least one measurement of CFS at 12 months (± 45 days) after initiation.

Safety analysis set (SAS): N /A.

5.7.2. Statistical methods

The general approach will be to test the difference in the response variable (CFS value) before and after initiation of treatment with Ikervis®. Initial exploratory analyses will utilise the Wilcoxon signed rank test to identify potentially significant changes in response. These will be augmented by the use of linear regression models that account for covariates (more important at smaller sample sizes) as well as confounding. The exact form of these models, such as the error distribution and link function of choice will be guided by the available data.

For all analyses, the amount of missing information will be described. In particular, if a significant degree of missing/inconsistent information is present in the data informing the primary endpoint (i.e. more than 15% of patients excluded from analysis), a comparison of patient characteristics among those with and without missing information will be conducted to assess the generalizability of the main results. Additionally, the rate of refusal per study site will be presented.

For all tests of statistical significance, formulation will be two-sided, and will be assessed at a significance level of 5%.

Primary endpoint

The primary analysis will be a comparison of the CFS grade at baseline with the CFS grade at 12 months after Ikervis® treatment start.

CFS grade at baseline and at 12 months post Ikervis® initiation, as well as change in CFS after 12 months of treatment, will be summarised by their mode as these are ordinal variables. A Wilcoxon signed rank test will be conducted to assess statistical significance of the change in CFS grade.

The primary endpoint will also be estimated as a baseline adjusted change using a logistic regression model. In this model, log odds ratio of an improvement in CFS grade will be modelled as a function of the baseline grade and relevant covariates. Covariates may include, but not be limited to, the following variables: country, age, gender, clinical signs at baseline (eyelid and conjunctival erythema, corneal fluorescein staining results, Schirmer's test result, tear film breakup time), as well as change in signs from baseline to 12 months post Ikervis® initiation.

Results will be presented overall and according to relevant subgroups (Previous steroid user / non users).

Secondary endpoints

Secondary endpoints will be presented descriptively. Continuous Data will be summarised with the use of means, standard deviation, minimum, maximum, median and number of valid values.

For categorical data such as gender and age categories, counts and proportions will be used to summarise the data. Categorical variables will be compared between subgroups using the Chi-squared test if the total of each class studied is greater than 5, otherwise Fisher's exact test will be used.

Several secondary outcomes are expressed as numbers or ordinal scales, these include tolerability scales and effectiveness scales. A negative binomial model will be used to model these data, with subgroup included as a factor.

5.7.3. Preliminary analysis

Preliminary analyses may be performed over the course of the study.

5.7.4. Sequential safety analysis/safety monitoring

N/A

5.8. Quality control

Before beginning data collection, all sites or CRO staff members will receive training on study procedures and completion of the eCRF. Remote monitoring of recorded data will be conducted for each site throughout the study. The value of periodic monitoring will be in that records with errors can be flagged and corrected. It is anticipated that monitoring will be performed on 20% of records; this will be tracked electronically.

5.8.1. Monitoring procedures

The ICON site manager will conduct in-house monitoring activities as needed during the study.

In-house site management activities will include site contact, generation of contact reports, site status tracking, attendance at team meetings, attendance at team training, responding to site questions, maintenance of updated investigator regulatory documents, issue resolution from previous site monitoring visits/calls, assisting with data queries, planning next calls, generation of reports, assist as needed with mass distribution of information, and maintaining the investigator file. ICON will maintain telephone contact with sites on a regular basis throughout the study.

Adverse events, SAEs, their follow up and reconciliation as needed shall remain the responsibility of Santen.

5.8.2. Critical documents

Before the physician starts the study (which is when informed consent is obtained from the first patient), the following documents must be available to Santen:

- Regulatory approval and/or notification as required

- Documentation of the physician's qualifications as medically qualified (for instance a short curriculum vitae or authorisation)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement
- Non-interventional study agreement
- Source document agreement

5.8.3. Retention of study documents

Santen will comply with Good Pharmacoepidemiological Practice (GPP) and relevant national legislation related to archiving of study documentation.

The physician must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The physician should not destroy any documents without prior permission from Santen.

Santen will retain the documentation pertaining to the study according to company procedures and in accordance with national regulations if they require a longer retention period.

6. Protection of human subjects

The study will be conducted in accordance with GPP, ISPE guideline for Good Pharmacoepidemiology Practices.[21]

6.1. Informed consent form for study patients

A voluntary, signed and personally dated, informed consent form will be obtained from the patient prior to any study-related activity.

The physician must give the patient information in a form that the patient can read and understand. This includes the use of an impartial witness where required.

In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki.

The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must also sign and date the patient information/informed consent form.

6.2. Data handling

If a patient withdraws previously given informed consent to participate in the study, that patient's data that has already been collected will be archived but will not be used in data analyses.

6.3. Premature termination of the study

The sponsor, physician or a pertinent regulatory authority may decide to stop the study or part of the study at any time, but agreement on procedures to be followed must be obtained.

Unplanned discontinuation of the study will be characterised by permanent suspension of data collection and other study-related activities.

If a study is prematurely terminated or suspended, information must be provided to the relevant national bodies as required by national regulation and procedure.

6.4. Responsibilities

6.4.1. Overall responsibility for the project and scientific queries related to Ikervis®

Santen

Feride Sahin
Director, Medical Affairs Europe
Medical Affairs CH
Santen Switzerland SA
La Voie-Creuse 14, 1202 Genève, Switzerland

e-mail: feride.sahin@santen.com

Mob.: +41 79 749 23 67

6.4.2. Reports and documentation of adverse events

Santen Oy Pharmacovigilance Unit

Niittyhaankatu 20, PO Box 33
33721 Tampere
Finland

e-mail: safetyEU@santen.com

Tel.: +358 3 284 8625 (24 hour)

Fax: +358 3 318 1060

6.4.3. Planning, preparation, technical project organization, data management and analysis, reporting

ICON

Marlene Gallopin-Bertrand
Project Manager
ICON Clinical Research
Direct : +33 1 30 45 06 04
Email: Marlene.Gallopin@iconplc.com

7. Managing and reporting of safety information

Adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Santen has the duty to collect all AEs that occur at the time of medical treatment in the non-interventional study **irrespective whether a causal link with Ikervis® is assumed or not**.

All investigators in the non-interventional study with Ikervis® shall be obligated to ensure that all AEs observed during the study are carefully recorded.

AE reporting forms shall be used to record all non-serious and serious cases of AEs that occurred or are observed during the non-interventional study, including:

- **already known AEs (for details see SPC)**
- **unexpected AEs**

Serious AEs shall be entered into the eCRF immediately, at the latest within 24 hours after the investigator/site staff became aware of the AE. Non-serious AEs shall be entered into the eCRF within 3 business days of awareness by the investigator/study site staff. All the relevant information related to the AE shall be recorded into the eCRF. It is particularly important to provide:

Causality assessment

- **I**t shall be assessed if the AE is possibly related or not related to Ikervis®

Seriousness assessment

- The AE is classified as **serious** when it
    - is fatal,
    - is life-threatening,
    - requires an in-patient treatment or extension of an in-patient treatment,
    - leads to a permanent or serious disability or invalidity,
    - is sight-threatening,
    - is an important medical event,
    - or represents a congenital anomaly or a birth defect.

Severity assessment

The investigator shall evaluate the severity of all AEs as follows**:**

- Mild: awareness of sign/symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity

- Severe: incapacitating sign/symptom with inability to work or do usual activity

Relevant concomitant conditions/medications

- All concomitant conditions/medications which may have a relation to AE shall be reported.

All AE reports will identify patients by unique code numbers assigned to the study patients, rather than by the patients' names, personal identification numbers, or addresses.

The entry into the eCRF will trigger an e-mail alert to Santen Pharmacovigilance Unit with the details of the event.

Santen Pharmacovigilance Unit will report suspected adverse reactions to regulatory authorities according to applicable regulatory requirements.

In addition, any information on the following events, regardless whether with or without AE, constitute collectable Safety Information and shall be recorded into eCRF (or in other format if separately instructed) within 3 business days of awareness by the investigator/study site staff:

- Misuse
- Overdose
- Medication error (including potential medication errors)
- Off-label use
- Exposure during pregnancy via mother or father
- Exposure during lactation
- Lack of or reduced therapeutic effectiveness
- Abuse
- Occupational exposure
- Suspected or confirmed transmission of an infectious agent via a medicinal product
- Suspected or confirmed interaction with another medicinal product or other interaction
- Suspected falsified medicinal products
- Unexpected therapeutic or clinical benefit

Santen will submit to regulatory authorities and ethic committees notification of emerging safety issues, if required. Santen will also provide annual and/or periodic safety reports to regulatory authorities.

All collected adverse events will be summarised as part of any interim safety analysis and in the final study report, where applicable.

8. Plans for dissemination and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Santen for regulatory purposes and for safety surveillance. All information supplied by Santen in connection with this study must remain the sole property of Santen and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Santen. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Santen.

8.1. Registration of study information

This study is eligible for registration at The EU PAS register.

If disclosure of non-interventional studies is mandatory in local study registries, the study will be registered in the appropriate registries according to local regulations.

8.2. Communication and publication

In accordance with Santen standard practice, key data from this study will be presented at a recognised congress and/or published in a peer-reviewed journal. Santen will work with a study publication steering committee and, as required, medical writers to develop the publications.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

The physician must ensure submission of the results of the study (either abstracts or full study report) to IEC/IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the physicians' and Santen's opinions must be fairly and sufficiently represented in the publication.

Santen maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol, to ensure the scientific accuracy of the data. Any such communication must be submitted in writing to the Santen study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

9. References

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10. Amendment log

Section	Original text	Amended text
Title	Ciclosporin 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting	~~**Ciclosporin**~~**Cyclosporine** 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting
1.1	Ciclosporin 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting.	~~**Ciclosporin**~~**Cyclosporine** 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting.
1.2	Ikervis® is a 1mg/mL ciclosporin eye drops emulsion for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.	Ikervis® is a 1mg/mL ~~ciclosporin~~**cyclosporine** eye drops emulsion for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.
1.4.1	The baseline value shall be measured after obtaining informed consent and within 7 days before the start of Ikervis® treatment.	The baseline value **will be collected and** shall be measured **only** after obtaining informed consent and within 7 days before the start of Ikervis® treatment.
1.4.2	• Schirmer's test Optional • Mean change in Visual acuity test (VA)	• Schirmer's test **without anaesthesia.** Optional • Mean change in Visual acuity ~~**test**~~ (VA)
1.5	Visit 1: Baseline visit with 7 days before the start of first Ikervis® prescription	Visit 1: Baseline visit with**in** 7 days before the start of first Ikervis® prescription
1.6.3	1.6.3. Minimum available data:	Minimum ~~**available**~~**required** data:

Section	Original text	Amended text

1.7.1	• Demographic data
	• Type and duration of prior treatment
	• CFS (Oxford scale grade)
	  ○ 0
	  ○ I
	  ○ II
	  ○ III
	  ○ IV
	  ○ V
	• Evaluation of subjective symptoms: foreign body sensation, burning/stinging, itching, pain, sticky feeling, blurred vision and photophobia
	• Evaluation of clinical signs under prior treatment
	• Reason(s) for change of medical therapy (effectiveness evaluation of prior treatment)
	• Any associated systemic disease (Diabetes, Rheumatologic diseases, Sjogren syndrome)
	• Systemic therapies
	• Topical steroid use: type, dose and duration of use
	• Topical ocular therapies, other than steroids
		• **Demographic data**
		  – **Gender**
		  – **Date of birth**
		• **Type of prior treatment and duration of use (both topical and systemic)**
		• **CFS at baseline (Oxford scale grade)**
		  – **0**
		  – **I**
		  – **II**
		  – **III**
		  – **IV**
		  – **V**
		• **Evaluation of subjective symptoms under prior treatment.**
		Severity categorised as none, mild, moderate, severe.
		  – **foreign body sensation**
		  – **burning/stinging**
		  – **itching**
		  – **pain**
		  – **sticky feeling**
		  – **blurred vision**

Section	Original text	Amended text
		– **photophobia** • **Evaluation of clinical signs under prior treatment** – **Schirmer's test without anaesthesia. Optional** – **Tear break up time (TBUT). Optional** – **Eyelid erythema** ▪ **None** ▪ **Mild** ▪ **Moderate** ▪ **Severe** – **Conjunctival erythema** ▪ **None** ▪ **Mild** ▪ **Moderate** ▪ **Severe** • **Visual acuity test** • **Use of artificial tears** – **Number of drugs** – **Frequency of use** • **Reason(s) for change of medical therapy (effectiveness evaluation of prior treatment)** – **Insufficient keratitis / dry eye disease control with prior medication**

Section	Original text	Amended text
		– **Progression of keratitis / dry eye disease** – **Poor local tolerance** – **Poor compliance** – **Other reasons** • **Any systemic disease** • **Systemic therapies** – **Yes / No** – **Name** – **Dose and duration of use** – **Indication** • **Topical ocular therapies** – **Yes / No** – **Name** – **Dose and duration of use** – **Indication** • **Adverse events during the study** • ~~**Demographic data**~~ • ~~**Type and duration of prior treatment**~~ • ~~**CFS (Oxford scale grade)**~~ ○ ~~**0**~~ ○ ~~**I**~~ ○ ~~**II**~~ ○ ~~**III**~~ ○ ~~**IV**~~

Section	Original text	Amended text
		~~V~~ • ~~Evaluation of subjective symptoms: foreign body sensation, burning/stinging, itching, pain, sticky feeling, blurred vision and photophobia~~ • ~~Evaluation of clinical signs under prior treatment~~ • ~~Reason(s) for change of medical therapy (effectiveness evaluation of prior treatment)~~ • ~~Any associated systemic disease (Diabetes, Rheumatologic diseases, Sjogren syndrome)~~ • ~~Systemic therapies~~ • ~~Topical steroid use: type, dose and duration of use~~ • ~~Topical ocular therapies, other than steroids~~
1.7.2	• CFS (Oxford scale grade) – 0 – I – II – III – IV – V • Evaluation of subjective symptoms: foreign body sensation, burning/stinging, itching, pain, sticky feeling, blurred vision and photophobia	• **CFS at current visit: (Oxford scale grade)** – **0** – **I** – **II** – **III** – **IV** – **V** • **Evaluation of subjective symptoms under prior treatment** **Severity categorised as none, mild, moderate, severe.**

Section	Original text	Amended text
	• Evaluation of clinical signs under Ikervis® treatment • Use of Artificial Tears (number of drugs, times per day) • Reason(s) for discontinuation of Ikervis®, if applicable • Concomitant therapies (topical ocular and systemic) • Steroid use: still using (yes/no) and if yes, dose • Documentation of adverse events during the study	– **foreign body sensation** – **burning/stinging** – **itching** – **pain** – **sticky feeling** – **blurred vision** – **photophobia** • **Evaluation of clinical signs under Ikervis® treatment** – **Schirmer's test without anaesthesia. Optional** – **Tear break up time (TBUT) Optional** – **Eyelid erythema** ▪ **None** ▪ **Mild** ▪ **Moderate** ▪ **Severe** – **Conjunctival erythema** ▪ **None** ▪ **Mild** ▪ **Moderate** ▪ **Severe** • **Visual acuity test**

Section	Original text	Amended text
		• **Use of artificial tears** – **Number of drugs** – **Frequency of use** • **Reason(s) for discontinuation of Ikervis®, if applicable** – **Insufficient keratitis / dry eye disease control with prior medication** – **Progression of keratitis / dry eye disease** – **Poor local tolerance** – **Poor compliance** – **Other reasons** • **Systemic therapies** – **Yes / No** – **Name** – **Dose and duration of use** – **Indication** • **Topical ocular therapies** – **Yes / No** – **Name** – **Dose and duration of use** – **Indication** • **Documentation of adverse events during the study**

Section	Original text	Amended text
		~~• CFS (Oxford scale grade)~~ ~~0~~ ~~I~~ ~~II~~ ~~III~~ ~~IV~~ ~~V~~ ~~• Evaluation of subjective symptoms: foreign body sensation, burning/stinging, itching, pain, sticky feeling, blurred vision and photophobia~~ ~~• Evaluation of clinical signs under Ikervis® treatment~~ ~~• Use of Artificial Tears (number of drugs, times per day)~~ ~~• Reason(s) for discontinuation of Ikervis®, if applicable~~ ~~• Concomitant therapies (topical ocular and systemic)~~ ~~• Steroid use: still using (yes/no) and if yes, dose~~ ~~Documentation of adverse events during the study~~
1.9	Approximately 1630 patients will be enrolled from study sites in five countries.	~~Approximately 1630~~**The planned enrolment target is approximately 400 patients** ~~**will be enrolled**~~ from study sites in five countries.

Section	Original text	Amended text
1.10	The primary analysis will be a comparison of the grade of CFS at baseline with that at 12 months after Ikervis® initiation. Where data on both eyes is available, both will be recorded and the CFS assessment for the worst eye at baseline used in the analysis.	The primary analysis will be a comparison of the grade of CFS at baseline with that at 12 months after Ikervis® initiation. Where data on both eyes is available, both will be recorded and the CFS assessment for the worst eye at baseline used in the analysis**, defined as the eye with the worst CFS grade at baseline. If both eyes have the same CFS grade then data from the right eye will be used**.
2.	This study was an open-label, non-randomized, one-arm, 24-month study extension of the Sansika Study. 67 patients were enrolled (37.9% of the 177 patients having ended Sansika). Treatment depends on disease severity. Currently available medical options include artificial tear products, lubricants, topical steroids and ciclosporin A (CsA).	This study was an open-label, non-randomized, one-arm, 24-month study extension of the **~~Sansika~~ SANSIKA** Study. 67 patients were enrolled (37.9% of the 177 patients having ended **~~Sansika~~SANSIKA**). Treatment depends on disease severity. Currently available medical options include artificial tear products, lubricants, topical steroids and **~~ciclosporin~~cyclosporine** A (CsA).
3.2	• To assess tear production using Schirmer's test	• To assess tear production using Schirmer's test **without anaesthesia**
5.1.1	The baseline value shall be measured after obtaining informed consent and within 7 days before the start of Ikervis® treatment.	The baseline value **will be collected** and shall be measured **only** after obtaining informed consent and within 7 days before the start of Ikervis® treatment.
5.1.2	• Mean change in Schirmer's test. Optional • Mean change in Visual acuity test (VA) All secondary endpoints will be assessed for the whole patient group and separately in specific subgroups	• Mean change in Schirmer's test **without anaesthesia**. Optional • Mean change in Visual acuity **~~test~~** (VA) All secondary endpoints will be assessed for the whole

Section	Original text	Amended text
	(Previous steroid user / non users, patients with and without associated systemic disease).	patient group and separately in specific subgroups (Previous steroid user / non users~~, patients with and without associated systemic disease~~).
5.1.3.4	The following details must be specified in the eCRF: • Starting date of medical treatment with Ikervis® • Prior medication and duration • Details of any concomitant therapy in addition to the use of Ikervis®	The following details must be specified in the eCRF: • Starting date of medical treatment with Ikervis® • ~~Prior medication and duration~~ • **Prior and concomitant medication , indication, duration and dosage** • ~~Details of any concomitant therapy in addition to the use of Ikervis®~~
5.2.1	Planned number of patients to be included: 1630 Planned number of patients to be included in the primary analysis: 1630	Planned number of patients to be included: ~~**1630**~~ **approximately** 400 Planned number of patients to be included in the primary analysis: ~~**1630**~~ **approximately** 400
5.2.4	5.2.4. Minimum available data:	5.2.4. Minimum ~~**available**~~required data:
5.2.7	The study accrual period will be determined based on the number of clinics recruited to achieve the current study goals. Collection of data for eligible patients will be undertaken between approximately March 2017 and March 2019, assuming a sufficient number of clinics to provide data for 1630 patients. During the recruitment period all eligible patients attending participating clinics will be invited to participate in the study, and if patients provide informed consent, relevant data will be recorded during routine clinical visits.	The study accrual period will be determined based on the number of clinics recruited to achieve the current study goals. Collection of data for eligible patients will be undertaken between approximately March 2017 and ~~**March**~~**November** 2019, assuming a sufficient number of clinics to provide data for ~~**1630**~~ **approximately 400** patients. During the recruitment period all eligible patients attending participating clinics will be invited to participate in the study, and if patients provide informed consent, relevant data will be recorded during routine clinical visits.

Section	Original text	Amended text
5.3.1	• Evaluation of clinical signs under prior treatment – Schirmer's test. Optional • Any associated systemic disease (Diabetes, Rheumatologic diseases, Sjogren syndrome) • Systemic therapies – Yes / No – Name • Topical steroid use – Yes / No – Type – Dose and duration of use • Topical ocular therapies, other than steroids – Yes / No – Type – Dose and duration of use	• Evaluation of clinical signs under prior treatment – Schirmer's test **without anaesthesia**. Optional • **Visual acuity test** • Any ~~**associated**~~ systemic disease ~~**(Diabetes, Rheumatologic diseases, Sjogren syndrome)**~~ • Systemic therapies – Yes / No – Name – **Dose and duration of use** – **Indication** • Topical **ocular** ~~**steroid use**~~**therapies** – **Yes / No** – **Name** – **Dose and duration of use** – **Indication** ~~– **Yes / No**~~ ~~– **Type**~~ ~~– **Dose and duration of use**~~

Section	Original text	Amended text
		• ~~**Topical ocular therapies, other than steroids**~~ – ~~**Yes / No**~~ – ~~**Type**~~ – ~~**Dose and duration of use**~~
5.3.2	• Evaluation of clinical signs under Ikervis® treatment – Schirmer's test Optional • Systemic therapies – Yes / No – Type – Dose – Duration of use • Topical steroid use – Yes / No – Type – Dose – Duration of use • Topical ocular therapies, other than steroids – Yes / No – Type	• Evaluation of clinical signs under Ikervis® treatment – Schirmer's test **without anaesthesia.** Optional • **Visual acuity test** • Systemic therapies – Yes / No – ~~**Type**~~**Name** – Dose **and duration of use** – ~~**Duration of use**~~**Indication** • Topical **ocular** ~~**steroid use**~~**therapies** – **Yes / No** – **Name** – **Dose and duration of use** – **Indication** ~~**Yes / No**~~ – ~~**Type**~~

Section	Original text	Amended text
	– Dose – Duration of use	~~**Dose**~~ ~~**Duration of use**~~ • ~~**Topical ocular therapies, other than steroids**~~ ~~**Yes / No**~~ ~~**Type**~~ ~~**Dose**~~ ~~**Duration of use**~~
5.5	This study aims to evaluate CFS at 12 months after Ikervis® initiation in routine clinical practice. Results can be presented by specific subgroups (e.g. according to the treatment immediately preceding Ikervis® start). For each patient group/subgroup, the sample size is based on the expected proportion of patients experiencing an improvement in the grade of CFS between the start of Ikervis® treatment and 12 months later. . Table 1 below describes the potential sample sizes required to detect a minimum odds ratio of CFS improvement, tested using a logistic regression and considering a significance level of 0.05. A range of possible minimum odds ratios are used (OR) (ranging from 2 to 8) and power (ranging from 80% to 95%). A reference odds ratio of 7.5 was chosen as the CFS response rate observed in the previous Ikervis® Phase III study NVG06C103.	This **is an observational** study~~**aims to evaluate CFS at 12 months after**~~**, carried out with the objective of assessing the effectiveness of** Ikervis® **in controlling severe keratitis, as measured by corneal fluorescein staining (CFS) improvement from baseline to 12 months from treatment** initiation**, in patients who have not improved despite treatment with tear substitutes,** in routine clinical practice. ~~**Results can be presented by**~~ **As such, the study is not setting out to test any** specific ~~**subgroups (e.g. according to the treatment immediately preceding Ikervis® start). For each patient group/subgroup**~~**hypothesis, but rather to be hypothesis generating. Consequently**, the sample size ~~**is based on the expected**~~**information provided here is offered in order to provide an approximate indication of the number of patients required in order to estimate the proportion of patients achieving a 1, 2 or 3 grade improvement in the primary outcome, i.e. their CFS**

Section	Original text	Amended text
		score (the response rate), as measured on the Oxford grading scale, at 12 months (+/- 45 days) from baseline.

Power (%)	**OR**				
	2	**4**	**6**	**7.5**	**8**
80	190	28	13	10	9
85	217	33	15	11	10
90	254	38	18	13	12
95	314	47	22	16	14

Based on the calculations above, an assessment of the primary outcomes with a power of 80% can be achieved with a minimum of 10 patients with complete data in each group.

When considering subgroup analyses, it is assumed that 60% of patients would previously have been on steroid treatment.

To allow for an analysis in the subgroup with systemic disease, the number of patients with complete data will be 17 (i.e. 10/0.60). The group expected to be observed least frequently (i.e. those with systemic disease) is chosen for sample size calculation to ensure that there are enough patients in the least frequently prescribed regimen group. As it is expected that 15% of the patients included could have inconsistent data, a minimum of 23 (i.e. 17/0.76) patients

The largest sample size required to achieve a specified margin of error around the estimated proportion achieving a particular number of grades improvement will always occur if 50% of the population achieve this level. The required sample size reduces at higher or lower response rates (Figure 1).

<Figure 1 inserted>

From the SANSIKA study (Baudouin et al. Eur J Ophthalmol 2017; 27(6): 678-685), the proportion of patients experiencing an improvement in ~~**the grade of CFS between the start of Ikervis® treatment and 12 months later. .**~~**CFS response of ≥ 2 grades or ≥ 3 following 12 months of treatment with 0.1% cyclosporine A cationic emulsion has previously been showed to be 66% and 42% respectively.**

~~**Table 1 below describes the potential sample sizes required to detect a minimum odds ratio of CFS improvement, tested using a logistic regression and considering a significance level of 0.05. A range of possible minimum odds ratios are used (OR) (ranging from 2 to 8) and power (ranging from 80% to 95%). A reference odds ratio of 7.5 was chosen as the CFS response rate observed in the previous Ikervis® Phase III study NVG06C103.**~~

<table>
<tr><td>Section</td><td>Original text</td><td>Amended text</td></tr>
<tr><td></td><td>will be included to ensure a sufficient sample to detect the CFS difference separately in all patients, and by pre-Ikervis® treatment subgroup. Therefore the total number of patients to be included is approximately 23.</td><td>
<table>
<tr><td rowspan="2"><s>Power (%)</s></td><td colspan="5"><s>OR</s></td></tr>
<tr><td><s>2</s></td><td><s>4</s></td><td><s>6</s></td><td><s>7.5</s></td><td><s>8</s></td></tr>
<tr><td><s>80</s></td><td><s>190</s></td><td><s>28</s></td><td><s>13</s></td><td><s>10</s></td><td><s>9</s></td></tr>
<tr><td><s>85</s></td><td><s>217</s></td><td><s>33</s></td><td><s>15</s></td><td><s>11</s></td><td><s>10</s></td></tr>
<tr><td><s>90</s></td><td><s>254</s></td><td><s>38</s></td><td><s>18</s></td><td><s>13</s></td><td><s>12</s></td></tr>
<tr><td><s>95</s></td><td><s>314</s></td><td><s>47</s></td><td><s>22</s></td><td><s>16</s></td><td><s>14</s></td></tr>
</table>

Based on <s>the calculations above, an assessment of the primary outcomes with a power of 80% can be achieved with a minimum of 10 patients with complete data in each group.</s>

<s>When considering subgroup analyses,</s>market research data it is assumed that 60% of patients would previously have been on steroid treatment.

<s>To allow for an analysis in the subgroup with systemic disease, the number of patients with complete data will be 17 (i.e. 10/0.60). The group expected to be observed least frequently (i.e. those with systemic disease) is chosen for sample size calculation to ensure that there are enough patients in the least frequently prescribed regimen group. As it is expected that 15% of the patients included could have inconsistent data, a minimum of 23 (i.e. 17/0.76) patients will be included to ensure a sufficient sample to detect the CFS difference separately in all patients, and by pre-Ikervis® treatment</s>
</td></tr>
</table>

Section	Original text	Amended text
		~~**subgroup. Therefore the total number of patients to be included is approximately 23.**~~**Based on former experience with observational studies it is assumed that 26% of patient records are dropped as a result of inconsistencies data.** **Then in order to be able to estimate the proportion of patients responding with a 1+, 2+ or 3+ grade improvement, with approximately a 9% margin of error around each estimate, the planned enrolment target is approximately 400 patients to cover all potential response rates.**
5.7.2	Results will be presented overall, and according to relevant subgroups, (Previous steroid user / non users) and country.	Results will be presented overall~~,~~ and according to relevant subgroups~~,~~ (Previous steroid user / non users) ~~**and country**~~**.**
6.4.3	Maria Luisa Mesa, PharmD Project Manager II ICON Clinical Research Mobile Phone: +34 600 401 606 Fax: +34 91 114 1290 Email: MariaLuisa,Mesa@iconplc.com	~~**Maria Luisa Mesa, PharmD**~~ ~~**Project Manager II**~~ ~~**ICON Clinical Research**~~ ~~**Mobile Phone: +34 600 401 606**~~ ~~**Fax: +34 91 114 1290**~~ ~~**Email: MariaLuisa,Mesa@iconplc.com**~~ **Marlene Gallopin-Bertrand** **Project Manager** **ICON Clinical Research** **Direct : +33 1 30 45 06 04** **Email: Marlene.Gallopin@iconplc.com**
7	7. Managing and reporting of adverse episodes/adverse	7. Managing and reporting of ~~**adverse episodes/adverse**~~

Section	Original text	Amended text
	reactions Santen has the duty to collect adverse events (AEs)that occur at the time of medical treatment **irrespective whether a causal link is assumed or not**. All participants in the non-interventional study with Ikervis® shall be obligated to ensure that all adverse AEs observed during the study are carefully recorded. AE reporting forms shall be used to record all non-serious and serious cases of AEs that occurred or are observed during the non-interventional study, including: • **already known AEs (for details see SPC)** and • **unexpected AEs** AEs shall be entered into the eCRF immediately at the latest within 24 hours after the physician became aware of the AE (for evaluation of Santen Pharmacovigilance Unit). All the relevant information related to the AE shall be recorded into the eCRF. It is particularly important to provide: **Causality assessment** - **I**t shall be assessed if the AE is possibly related or not related to Ikervis® **Seriousness assessment** - The AE is classified as **serious** when it is fatal, life-	**~~reactions~~safety information** **Adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.** Santen has the duty to collect **~~adverse events (~~**all AEs**~~)~~** that occur at the time of medical treatment **in the non-interventional study** irrespective whether a causal link **with Ikervis®** is assumed or not. All **~~participants~~investigators** in the non-interventional study with Ikervis® shall be obligated to ensure that all **~~adverse~~** AEs observed during the study are carefully recorded. AE reporting forms shall be used to record all non-serious and serious cases of AEs that occurred or are observed during the non-interventional study, including: • **already known AEs (for details see SPC)** **~~and~~** • **unexpected AEs** **Serious** AEs shall be entered into the eCRF immediately, at the latest within 24 hours after the **~~physician~~investigator/site staff** became aware of the AE **~~(for evaluation~~**. **Non-serious AEs shall be entered into the eCRF within 3 business days** of **~~Santen Pharmacovigilance Unit).~~awareness by the investigator/study site staff.** All the relevant information

Section	Original text	Amended text
	threatening or sight-threatening, requires an in-patient treatment or extension of an in-patient treatment, leads to a permanent or serious disability or invalidity or represents a congenital anomaly or a birth defect. **Severity assessment** The investigator shall evaluate the severity of all AEs as follows**:** - Mild: awareness of sign/symptom, but easily tolerated - Moderate: discomfort enough to cause interference with usual activity - Severe: incapacitating sign/symptom with inability to work or do usual activity **Relevant concomitant conditions/medications** - All concomitant conditions/medications which may have a relation to AE shall be reported. Any AE or SAE which occurs during this study must be recorded by the Investigator/site staff within 24 hours in the eCRF. Entry into the eCRF will trigger an e-mail alert to Santen Medical Safety with the details of the event. Line listings of all non-serious AEs and Serious AEs will be created by Data Management and sent to Santen PVU for	related to the AE shall be recorded into the eCRF. It is particularly important to provide: **Causality assessment** - **I**t shall be assessed if the AE is possibly related or not related to Ikervis® **Seriousness assessment** - The AE is classified as serious when it o fatal, o is life-threatening, o requires an in-patient treatment or extension of an in-patient treatment, o leads to a permanent or serious disability or invalidity, o is sight-threatening, o is an important medical event, o or represents a congenital anomaly or a birth defect. **Severity assessment** The investigator shall evaluate the severity of all AEs as follows**:** - Mild: awareness of sign/symptom, but easily tolerated

Section	Original text	Amended text
	review and reconciliation with the safety database on a regular basis. In addition, the Investigator will report suspected adverse reactions to regulatory authorities, as required by pharmacovigilance practice regulations for marketed drug products All AE reports will identify patients by unique code numbers assigned to the study patients, rather than by the patients' names, personal identification numbers, or addresses. In addition, any information on the following events, regardless whether with or without AE, constitute collectable Safety Information and shall be recorded into eCRF: • Misuse • Overdose • Medication error • Off-label use • Exposure during pregnancy via mother or father • Exposure during lactation • Lack of or reduced therapeutic efficacy • Abuse • Occupational exposure	- Moderate: discomfort enough to cause interference with usual activity - Severe: incapacitating sign/symptom with inability to work or do usual activity **Relevant concomitant conditions/medications** - All concomitant conditions/medications which may have a relation to AE shall be reported. ~~**Any AE or SAE which occurs during this study must be recorded by the Investigator/site staff within 24 hours in the eCRF. Entry into the eCRF will trigger an e-mail alert to Santen Medical Safety with the details of the event.**~~ ~~**Line listings of all non-serious AEs and Serious AEs will be created by Data Management and sent to Santen PVU for review and reconciliation with the safety database on a regular basis.**~~ ~~**In addition, the Investigator will report suspected adverse reactions to regulatory authorities, as required by pharmacovigilance practice regulations for marketed drug products**~~ All AE reports will identify patients by unique code numbers assigned to the study patients, rather than by the patients' names, personal identification numbers, or addresses.

Section	Original text	Amended text
	• Suspected or confirmed transmission of an infectious agent via a medicinal product • Suspected or confirmed interaction with another medicinal product or other interaction • Suspected falsified medicinal products Santen will submit to regulatory authorities and ethic committees notification of emerging safety issues, if required. Santen will also provide annual and/or periodic safety reports to regulatory authorities.	**The entry into the eCRF will trigger an e-mail alert to Santen Pharmacovigilance Unit with the details of the event.** **Santen Pharmacovigilance Unit will report suspected adverse reactions to regulatory authorities according to applicable regulatory requirements.** In addition, any information on the following events, regardless whether with or without AE, constitute collectable Safety Information and shall be recorded into eCRF **(or in other format if separately instructed) within 3 business days of awareness by the investigator/study site staff**: • Misuse • Overdose • Medication error **(including potential medication errors)** • Off-label use • Exposure during pregnancy via mother or father • Exposure during lactation • Lack of or reduced therapeutic ~~**efficacy**~~effectiveness • Abuse

Section	Original text	Amended text
		• Occupational exposure • Suspected or confirmed transmission of an infectious agent via a medicinal product • Suspected or confirmed interaction with another medicinal product or other interaction • Suspected falsified medicinal products • **Unexpected therapeutic or clinical benefit** Santen will submit to regulatory authorities and ethic committees notification of emerging safety issues, if required. Santen will also provide annual and/or periodic safety reports to regulatory authorities. **All collected adverse events will be summarised as part of any interim safety analysis and in the final study report, where applicable.**
8.1	This study is eligible for registration at www.clinicaltrials.gov. If disclosure of non-interventional studies is mandatory in local study registries, the study will be registered in the appropriate registries according to local regulations. Note: Study registration is regarded as the publication of an internationally-agreed set of information (which can be found at the World Health Organization (WHO) homepage) about the design, conduct and administration of non-interventional studies. These details are published on a publicly-accessible website managed by a registry	This study is eligible for registration at ~~**www.clinicaltrials.gov.**~~ **The EU PAS register**. If disclosure of non-interventional studies is mandatory in local study registries, the study will be registered in the appropriate registries according to local regulations. ~~**Note: Study registration is regarded as the publication of an internationally-agreed set of information (which can be found at the World Health Organization (WHO) homepage) about the design, conduct and administration of non-interventional studies. These**~~

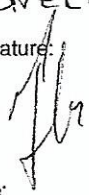
Section	Original text	Amended text
	conforming to WHO standards (also found at the WHO homepage); for example, www.clinicaltrials.gov. In accordance with Santen standard practice, topline study results will also be provided on EUDRAT / ClinicalTrials.gov.	~~**details are published on a publicly-accessible website managed by a registry conforming to WHO standards (also found at the WHO homepage); for example, www.clinicaltrials.gov.**~~ ~~**In accordance with Santen standard practice, topline study results will also be provided on EUDRAT / ClinicalTrials.gov.**~~

11. Final protocol sign off

Title: Cyclosporine 1mg/ml eye drop emulsion (Ikervis®) for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes: Clinical effectiveness, tolerability and safety in a real world setting.

Version: 3.0

Date: 04 April 2018

Santen representative	ICON representative
Name (Please print): Feride Sahin	Name (Please print): Richard Pitman
Position: Medical Affairs Director	Position: Lead Epidemiologist
Signature: 	Signature: 
Date: 25.05.2018	Date: 04 Apr 2018